DURK PEARSON & SANDY SHAW

Box 2160, Tonopah, NV 89049

TO: Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Second Comments for Docket No. 98N-0148

Before the
FOOD AND DRUG ADMINISTRATION
Rockville, MD

In re: International Drug Scheduling; Convention On Psychotropic Substances; Single Convention On Narcotic Drugs; World Health Organization Scheduling Recommendations for Ephedrine; Comments On Abuse Potential, Actual Abuse, Medical Usefulness, Usefulness as a Dietary Supplement Under DSHEA, and Trafficking in Ephedrine and Ephedra Sinica Herb; Limits to FDA Authority Under DSHEA; Limits to FDA's Authority to Accept and Adopt International Standards and Recommendations Fed. Reg. 64(6): 1629-1634 January 11, 1999	Docket No. 98N-0148 (Second Comments)

10 February, 1999

98N-0148

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INTRODUCTION TO COMMENTS OF DURK PEARSON & SANDY SHAW

Note: These comments pertain to ephedrine, ephedra herb, ephedra herb and ephedrine containing dietary supplements, the family of ephedra alkaloids found in ephedra sinica, and related isomers such as pseudoephedrine and phenylpropanolamine. No comments are hereby tendered regarding dihydroetorphine or remifentanyl.

Durk Pearson and Sandy Shaw are scientists and authors, maintaining residences in Nevada and California. Their three best-selling books include the million plus copy #1 best-seller Life Extension, a Practical Scientific Approach (Warner Books, 1982). Their fourth book, Freedom of Informed Choice: FDA v. Nutrient Supplements argues that truthful, non-misleading speech on labels and in labeling is protected by the First Amendment of the United States Constitution against FDA censorship and discusses the cost to public health of such censorship.

Commenters' First Amendment and APA (Administrative Procedure Act) arguments were recently vindicated by the 3-0 decision of the US Circuit Court of Appeals for the District of DC against the FDA on January 15, 1999 in Pearson and Shaw et al v. Shalala et al. (Case No. 98-5043)

Pearson and Shaw design dietary supplement formulations and license them to small marketing and manufacturing companies. The formulations designed by Pearson and Shaw include dietary supplements in the form of herbal teas containing ground ephedra herb leaves and stems. Pearson and Shaw and their licensed marketers and manufacturers (all are small businesses) would suffer substantial economic harm if the FDA were to recommend, and WHO were to implement, restrictions on the sale of ephedra herb itself or on DSHEA compliant dietary supplements containing ephedra herb. Furthermore, Pearson & Shaw believe that consumers of ephedra herb dietary supplements would be endangered, rather than helped, by any such restrictions.

COMMENTS OF DURK PEARSON & SANDY SHAW

We hereby include with and incorporate into these Comments our First Comments on 98N-0148 of 1 April 1998, and our very closely related and relevant prior Comments on 95N-0304 of 18 August 1997, and on 97N-0218 of 30 September 1997. (See attached.)

Abuse of Ephedra Herb Containing Dietary Supplement Teas is Not a Significant or Widespread Problem

FDA states that in the US, ephedrine and ephedrine containing combination products have been abused. To prepare for Commenters' Comments on 95N-0304 (see attached), the Commenters made a FOIA (Freedom Of Information Act) request on the FDA for all documents pertaining to the safety and abuse potential of ephedrine and ephedrine containing products, including OTC drugs and dietary supplements. The Commenters received several thousand pages of documents which clearly and unequivocally demonstrated that abuse of ephedrine and ephedrine containing products was not common, amounting at most to a few tens of cases per year out of several million non-abusing users each year. The reported abuse was almost entirely of OTC drug products, many of which were mislabeled or misbranded. At most, this abuse led to no more than a few deaths per year, and there was no evidence of abuse of ephedra herb containing dietary supplement teas.

This is a far smaller problem than the abuse of non-prescription NSAIDS (Non-Steroidal Anti-Inflammatory Drugs) such as aspirin, ibuprofen, and sodium naproxen which result in approximately 9,000 deaths per year in the US. Moreover, it is widely accepted by experts in the field that caffeine addiction is common among coffee consumers, and that anyone who consumes about 800 milligrams or more of caffeine per day will quickly become addicted, and suffer very severe headache pain for a week

or more during caffeine withdrawal. There are at least several hundred thousand caffeine addicts in the US. (See Caffeine and Behavior by B.S. Gupta and U. Gupta, CRC Press, 1999) Ephedrine abuse in the US is a far smaller problem than either the abuse of caffeine or NSAIDS, and abuse of dietary supplement teas containing ground whole ephedra herb is essentially non-existent.

In its request for comments, FDA states, "In addition, in the USA, combination products containing ephedrine in herbal preparations have been abused." The several thousand pages of documents that the Commenters received from the FDA in response to their 1997 FOIA did not contain evidence of abuse of ephedra herb tea. Capsules or tablets containing ephedrine are far more readily abused than the true ephedra herb teas licensed by the Commenters for reasons discussed in Commenters' comments to 95N-0304 and below.

Scientific Differences Between Ephedrine Containing OTC Drugs and Ephedra Herb Tea Dietary Supplements; Ephedra Herb Tea is Far Less Likely to be Abused:

It is very easy for a drug abuser to swallow several cheap 50 milligram ephedrine pills or 60 mg. pseudoephedrine pills, and to repeat this foolish act every hour. Because of this, there have been several reported hospitalizations due to overdoses of ephedrine or pseudoephedrine pills, and one overdose death. This frequency of abuse, hospitalizations, and death from misuse of ephedrine or pseudoephedrine tablets is far lower than the reported frequency of abuse, hospitalizations, and deaths from misuse of acetaminophen tablets (e.g. Tylenol^{R}). There is no rational scientific justification for limiting the availability of ephedra herb containing dietary supplements on the basis of their relatively low level of reported abuse. Finally, while it is quick and easy to take 10 ephedrine or pseudoephedrine tablets, it is not at all quick and easy to take 20 to 30 cups of ephedra herb dietary supplement tea containing the same amount of ephedrine.

Because of these prominent and fundamental scientific differences between ephedra herb tea dietary supplements and ephedrine or pseudoephedrine OTC tablets, there is no rational scientific basis for Scheduling ephedra herb tea dietary supplements.

In addition to the statutory prohibitions mentioned below against FDA's complicity in effectively banning (via supporting the proposed Scheduling) dietary supplement teas containing ephedra herb, there are compelling scientific reasons for distinguishing between ephedrine or pseudoephedrine containing OTC drugs and ephedra herb containing dietary supplement teas. Even if the proposed Scheduling is adopted for OTC drugs, the reasoning on which it is based is inapplicable to dietary supplement teas containing ephedra herb.

Ephedra Herb Containing Dietary Supplement Teas Are Not Subject to Diversion to Illegal Drug Manufacture.

There are **no** reported cases in the scientific or forensic literature of ephedra herb containing dietary supplement teas being diverted to the illicit manufacture of methamphetamine or methcathinone, whereas there have indeed been cases where hundreds of thousands of OTC ephedrine and pseudoephedrine pills have been subject to such diversion. The reason for this difference is simple. It is easy and highly profitable to convert OTC ephedrine and pseudoephedrine pills to methamphetamine, whereas it is extremely difficult and utterly unprofitable to perform such an illegal conversion using a dietary supplement tea containing ground ephedra herb as a precursor.

A typical ephedrine tablet may contain 50 milligrams of ephedrine (or 60 mg. pseudoephedrine in common OTCs) and 150 milligrams (180 mg.) of inert tablet filler-binder. The

ephedrine or pseudoephedrine content is 25%. The ephedrine and pseudoephedrine can be quickly, easily, and economically extracted from the tablets and separated from the inert and frequently insoluble tablet filler-binder using a small amount of solvent.

A typical ephedra herb containing dietary supplement tea contains 20 milligrams of ephedrine contained in about 2 grams of ground ephedra herb (the amount of which is varied to standardize the ephedrine content per serving of tea) which is mixed with 10 to 20 grams of other constituents consisting of 10 to 20 other herbs, spices, vitamins, minerals, flavor extracts, sugars, and other food ingredients. The ephedrine content of the herbal tea dietary supplements is typically 0.1% to 0.15%, not the 25% commonly found in ephedrine (or pseudoephedrine) tablets. Because of this, at least 200 times as much solvents would be required to extract the ephedrine from the mixture, and the illicit production equipment would have to be at least 200 times larger than would be required for extracting ephedrine from tablets. Extraction of 10 kilograms of ephedrine from 10,000 kilograms of herbal tea using 100,000 to 200,000 kilograms of solvents is not an operation that can be hidden in a garage or an apartment, completely unlike the case with ephedrine or pseudoephedrine tablets. Moreover, many of the other constituents of the herbal tea would be far more difficult to separate from the ephedrine, unlike simple tablet fillers and binders such as dicalcium phosphate.

In addition, a typical ephedra herbal tea dietary supplement sells for 50 cents to $1.00 per serving, a cost per milligram of contained ephedrine (or pseudoephedrine or phenylpropanolamine) that is about 10 to 100 times higher than ephedrine, pseudoephedrine, or phenylpropanolamine OTC tablets. When one considers the added cost of at least 200 times as much solvents, the difficulty of an illicit operation purchasing so much solvents without arousing suspicion, the cost of processing equipment that is at least 200 times larger, the far greater

difficulty, cost, and much lower efficiency of extracting the ephedrine from such a dilute complex mixture, and the difficulty and cost of hiding such large extraction and purification equipment and such large amounts of solvents (to say nothing of disposing of the 100 to 200 tons of used solvents afterward!), it is not surprising that ephedra herb tea dietary supplements have never been diverted to methamphetamine manufacture, and never will be.

Although ephedrine can be used in the illicit manufacture of methamphetamine, bulk sales of this substance are already controlled in the US by the DEA as a "listed chemical" precursor compound under the Controlled Substances Act. There is no record of ephedra herb ever being used as a precursor by illicit drug manufacturers. It would be economically impractical to do so as explained above and in Commenters' First Comments to 98N-0148 and Commenters' Comments to 95N-0304.

The WHO proposed Scheduling is irrational, arbitrary, and capricious because it will be completely ineffective unless pseudoephedrine and phenylpropanolamine are controlled at least as stringently as ephedrine:

Far more widely used than ephedra herb containing dietary supplement teas and ephedrine containing OTC drugs are OTC drugs that contain pseudoephedrine (e.g. Sudafed^{R}) and phenylpropanolamine. The same simple efficient palladium catalyzed hydrogenation (or the illicitly popular iodine-red phosphorus method) that converts ephedrine to methamphetamine will convert pseudoephedrine to methamphetamine and phenylpropanolamine to amphetamine with equal ease and efficiency. Pseudoephedrine is just as suitable as ephedrine as a precursor for the illicit manufacture of methcathinone, too. The amounts of pseudoephedrine and phenylpropanolamine used in the OTC drug industry are far larger than the amounts of ephedra herb used, hence any rule that restricts ephedra herb containing

dietary supplement teas but not pseudoephedrine and phenylpropanolamine OTC drugs is irrational, arbitrary, and capricious because it will be completely ineffective in controlling the supply of precursors for the manufacture of illicit methamphetamine, methcathinone, and amphetamine. Since there is very little problem with the abuse of pseudoephedrine and phenylpropanolamine OTC drugs, it is expected that the very large drug companies manufacturing these products will apply for and receive Convention Article 3, paragraph 2 or 3 exemptions to prescription requirements. Recommending that ephedra herb containing dietary supplement teas be Scheduled will therefore have no effect on either abuse or diversion to as precursors to illicit drug manufacture.

Because of these considerations, any FDA recommendations that do not reject the proposed Scheduling violates the Administrative Procedures Act and DSHEA (under which ephedra herb is a dietary supplement), and therefore must be rejected.

Neither the Law Nor the Facts Permits FDA to Recommend Adoption of the Proposed UN Scheduling Applicable to Ephedra Herb Containing Dietary Supplement Teas

On the basis of both the law (DSHEA and APA) and the administrative record of the facts, FDA cannot make any recommendation to the UN that would interfere with the manufacture, availability, and sale of properly labeled ephedra herb tea dietary supplements, for to do so would be arbitrary, capricious, not in accord with the facts, and contrary to law. Before FDA could make any recommendation to any international body that would interfere with the manufacture, availability, and sale of ephedra herb teas, FDA must first meet its DSHEA (Dietary Supplement Health and Education Act) burden of proof that properly labeled ephedra herb teas are unreasonably unsafe when used as directed. FDA has not met that burden of proof.

FDA does not have the constitutional legal authority to simply accede to the recommendation of an international organization that ephedrine containing products be Scheduled under international psychotropic convention drug laws in violation of U.S. statutes and the restrictions on federal power under the U.S. Constitution.

The Limits of Federal Authority Under Treaties

One legal argument on treaties is, of course, that a treaty cannot go beyond the bounds of the Constitution by, for example, giving away Constitutionally protected rights. As the U.S. Supreme Court ruled in **Geofroy v. Riggs** (1890): "The treaty power, as expressed in the Constitution, is in terms unlimited except by those restraints which are found in that instrument against the action of the government or of its departments, and those arising from the nature of the government itself and of that of the States. It would not be contended that it extends so far as to authorize what the Constitution forbids, or a change in the character of the government or in that of one of the States, or a cession of any portion of the territory of the latter, without its consent." In 1957 in **Reid v. Covert**, the Court ruled that "no agreement with a foreign nation can confer power on the Congress, or on any other branch of Government, which is free from the restraints of the Constitution." Moreover, the Court continued, "this Court has regularly and uniformly recognized the supremacy of the Constitution over a treaty."

An on-point argument as to why FDA cannot simply accede to the recommendations of an international agency can be found in a recent issue of the National Law Journal:

An analysis published in the March 17, 1997 National Law Journal (NLJ), Martin, Farber, Chajet "Determination on Silica May Expose Flaw in Rule," offers a Constitutional argument to oppose standards (such as the UN Scheduling of ephedra herb

containing dietary supplement products) supposedly binding upon the United States that are developed under the auspices of the United Nations. These legal arguments are equally applicable to the proposal that is the subject of this Comment.

The case of interest concerns an OSHA rule in which OSHA incorporated certain standards and findings (on silica -- ordinary sand -- as a carcinogen) that were developed by the International Agency for Research on Cancer (IARC). An important constitutional issue was raised in the article concerning the OSHA rule: whether an Executive agency which has received its rulemaking authority as a result of delegation by Congressional statute can re-delegate that authority to a third party. The Constitution states in Article I Section I: "All legislative powers herein granted shall be vested in a Congress of the United States..."

As the NLJ article noted: "...the agency [OSHA] has taken what is concededly a broad delegation of authority and effectively redelegated that authority to an extragovernmental entity." "Though OSHA may well have broad authority to decide issues under the OSH Act, it does not follow that the agency can pass that same authority to another entity."

The issue arose, though indirectly, in the context of a 1992 decision by the 11th U.S. Circuit Court of Appeals (AFL-CIO v. Occupational Safety and Health Administration 965 F.2d 962, 984 (11th Cir. 1992)), in which the Court considered the propriety of OSHA's incorporation into its rules of the standards and findings of an outside organization. In that case, the court vacated a "generic" OSHA rulemaking to set permissible exposure limits for 428 substances identified by the agency as air contaminants. "The court found that while OSHA may 'rely on the recommendations and documentation' of outside organizations (such as the "threshold limit values" established by the American Conference of Governmental Industrial Hygienists), the outside body's findings 'did not relieve OSHA of the responsibility for making

detailed findings, with adequate explanations for all statutory criteria.'"

The NLJ article then goes on to say "The inevitable debate over the marriage of OSHA regulations and the IARC silica findings may also spill over into the constitutional realm. Necessarily, Congress must delegate to the executive branch substantial, but not unbridled, authority to implement the policy judgments of the legislative branch. The undelegable essentials of the legislative function are the determination of the legislative policy and its formulation as a defined and binding rule of conduct."

Commenters have argued in their recently filed 108 pages of public comments on an FDA rulemaking concerning ephedra alkaloid containing dietary supplements (95N-0304) that the FDA cannot adopt the standards for ephedra herb dietary supplements set by the Canadian government because Canada is not bound by the U.S. Constitution, the U.S. Congress cannot delegate its Constitutional legislative powers to the Canadian government, the FDA cannot redelegate its rulemaking authority to the Canadian government, and the Canadian government is not bound by (among other things) the procedural requirements of the FACA (open meeting law) or the APA (Administrative Procedures Act). **All this applies as well to standards -- such as drug control schedules -- set by the United Nations.**

Note that the FDA's proposed rules on ephedra herb containing dietary supplements -- considered a high priority by the FDA -- were to go into effect in February 1998; however, the rules have not yet been issued because the FDA could not meet its burden of proof under DSHEA. FDA cannot legally take ephedra herb dietary supplement products off the market via the back door method of acceding to an international treaty which would effectively accomplish such removal without first meeting the DSHEA burden of proof that such dietary supplements, when properly labeled, are unreasonably unsafe when used as directed.

The Article 3, Paragraphs 2 and 3 Convention Exemption

FDA has stated that the 1971 UN Psychotropic Convention provides that "Under Article 3, paragraphs 2 and 3, a party may exempt from certain controls under the Convention, including the prescription requirement, if the preparation is compounded in such a way that it presents no, or a negligible, risk of abuse." **However, This provision is expressly applicable to drugs, not to dietary supplements. No dietary supplement has ever received an exemption under this provision.**

Adverse and Disparate Impact on Small Businesses and FDA Failure to Comply with Statutory Requirements Regarding Same

FDA has failed to fulfill its statutory obligation to consider the impact of this proposed regulatory action on small businesses. This failure is sufficient to require that the FDA exercise option #3, "reject the recommendations [regarding Scheduling ephedrine containing products] entirely." in its recommendations to WHO and CND (United Nations Commission on Narcotic Drugs.

Non-prescription medications containing pseudoephedrine are the most popular drugs in the US for the symptomatic relief of colds, flu, and allergies. The most popular brands are made by large corporations that may have the financial and legal resources to seek an Article 3, paragraph 2 or 3 exemption. The small businesses producing ephedra herb containing dietary supplements do not have these resources, and the failure of FDA to consider this difference in its Federal Register announcements of January 11, 1999, legally precludes the FDA from making any recommendation other than option #3, "reject the recommendations entirely."

CONCLUSION

DSHEA, APA, the scientific facts, constitutional limits on treaty powers and delegation, and statutes requiring assessment of regulatory impact on small businesses require that FDA adopt option #3; "reject the recommendations entirely."

Submitted 10 February 1999 by Durk Pearson & Sandy Shaw,

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&

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TO: Dockets Management Branch (HFA-305)
Food and Drug Administration
12410 Parklawn Dr., Rm. 1-23
Rockville, MD 20857
Comments for Docket No. 98N-0148

Before the
FOOD AND DRUG ADMINISTRATION
Rockville, MD

In re: Comments Concerning Abuse Potential, Actual Abuse, Medical Usefulness, Usefulness as a Dietary Supplement Under DSHEA, and Trafficking in Ephedrine and Ephedra Sinica Herb Fed. Reg. 63(52): 13258-13259 March 18, 1998	)	Docket No. 98N-0148

3 April, 1998

INTRODUCTION TO COMMENTS OF DURK PEARSON & SANDY SHAW

Note: These comments pertain to ephedrine, ephedra herb, ephedra herb and ephedrine containing dietary supplements, and the family of ephedra alkaloids found in ephedra sinica. No comments are hereby tendered regarding dihydroetorphine or remifentanyl. These comments apply to "isomers of psychotropic substances" only insofar as any FDA recommended WHO rules would apply to the family of ephedra alkaloids found in ephedra sinica.

Durk Pearson and Sandy Shaw are scientists and authors, maintaining residences in Nevada and California. Their three best-selling books include the million plus copy #1 best-seller Life Extension, a Practical Scientific Approach (Warner Books, 1982). Their fourth book, Freedom of Informed Choice: FDA v. Nutrient Supplements argues that truthful, non-misleading speech on labels and in labeling is protected by the First Amendment of the United States Constitution against FDA censorship and discusses the cost to public health of such censorship.

Pearson and Shaw design dietary supplement formulations and license them to small marketing and manufacturing companies. The formulations designed by Pearson and Shaw include dietary supplements containing ground ephedra herb leaves and stems. Pearson and Shaw and their licensed marketers and manufacturers (all are small businesses) would suffer substantial economic harm if the FDA were to recommend, and WHO were to implement, restrictions on the sale of ephedra herb itself or on DSHEA compliant dietary supplements containing ephedra herb. Furthermore, Pearson & Shaw believe that consumers of ephedra herb dietary supplements would actually be endangered by any such restrictions.

DSHEA (Dietary Supplement Health and Education Act) places a substantial statutory burden of proof on FDA to demonstrate that an herbal dietary supplement is unreasonably unsafe when used as directed before FDA is legally permitted to take any action to restrict or prohibit the sales of such a supplement or its ingredients. Under the provisions of DSHEA, FDA has no statutory authority to recommend that WHO restrict ephedra herb, ephedra herb containing dietary supplements, or their constituent ingredients unless FDA has met their DSHEA burden of proof.

Pearson & Shaw do not believe that the FDA has met their statutory burden of proof under DSHEA that ephedra herb and ephedrine containing and ephedra herb containing dietary supplements are unreasonably risky to consumers when used as

directed.

On the contrary, the evidence presented by the FDA's own Expert Committee on Ephedrine Alkaloid Containing Dietary Supplements (which we review at length in the attached 107 page public comment document previously filed by Pearson & Shaw with the FDA) shows that extant ephedra herb supplements with extant labeling are generally safer than food in common form. Please see Pearson & Shaw's 107 pages of Comments (attached). We filed these comments on FDA's Docket No.95N-0304: Dietary Supplements Containing Ephedrine Alkaloids, and they address the abuse potential, actual abuse, potential dangers, actual dangers, and usefulness as DSHEA regulated dietary supplements of ephedrine and ephedra herb containing products.

Note that the aforementioned FDA Expert Committee on Ephedrine Alkaloid Containing Dietary Supplements found that millions of Americans were using ephedrine containing dietary supplements. They identified only a few abusers among these many millions of American users, and found **no evidence of abuse of either ephedra herb itself or of ephedra herb containing dietary supplements.**

Re illicit trafficking:

There is no illicit trafficking in ephedra herb or in dietary supplements containing ephedra herb. Ephedrine itself has already been designated as a listed chemical and is subject to chemical diversion regulations under 21 CFR part 1310 which are enforced by the Drug Enforcement Administration, due to its potential for use as a precursor in illicit methamphetamine manufacturing.

Any recommendation by FDA to WHO (or any other party) that ephedra herb (or ephedra herb containing dietary supplements) be subject to the same restrictions as ephedrine itself would be

arbitrary, capricious, contrary to fact, and a violation of the Administrative Procedure Act.

There is no record of ephedra herb ever having been used as a precursor for illicit methamphetamine.

To make one kilogram of illicit methamphetamine would require about 1.5 kg. of ephedrine, and a few kilograms of other chemicals (e.g., red phosphorous) and solvents. The conversion would be performed in reaction vessels of a few liters volume, and the whole operation can be (and often has been) performed in a residential kitchen or bathroom.

To make 1 kg. of illicit methamphetamine from **ephedra herb**, however, would require that the ephedrine first be extracted from approximately **200 kg. of raw ephedra sinica herb** with the use of approximately **2,000 kg. of solvents** in an extraction vessel of approximately **3,000 liters** volume. Obviously, an operation of this scale cannot be readily hidden, and extraction solvent purchases of this magnitude would be both prohibitively expensive and highly suspicious, to say nothing of the difficulties involved in the illicit disposal of such huge amounts of used solvents. It is obvious, therefore, why ephedra herb has **never** been used as a source of ephedrine for illicit methamphetamine manufacture. It is also obvious that ephedra herb containing dietary supplements would be an even more difficult and less economic source of ephedrine than ephedra herb itself.

For these reasons, and additional reasons stated in the attached 107 pages of comments, **if FDA makes any recommendations to WHO regarding ephedrine, FDA must distinguish between ephedra herb (and DSHEA regulated dietary supplements containing ephedra herb) on the one hand and pure ephedrine on the other.**

RE:Docket No.98N-0148;International Drug Scheduling; ... Ephedrine...

FDA, in accord with U.S. law, must recommend to WHO that ephedra herb itself and ephedra herb containing dietary supplements <u>NOT</u> be subject to any additional regulation, and under no circumstances be regulated the same as ephedrine; any other recommendation would be a clear violation of the intent of the DSHEA and of the APA.

Sincerely,

Durk Pearson

Sandy Shaw

Before the
Department of Health and Human Services
Public Health Service
Food and Drug Administration

Docket No. 97N-0218
RIN 0910-ZA01

Consideration of Codex Alimentarius
Standards

ACTION: Advance notice of proposed rulemaking.
62 FR 36243, July 7, 1997

COMMENTS OF
DURK PEARSON AND SANDY SHAW

COMMENTERS Pearson and Shaw are scientists, maintaining residences in Nevada and California, who design dietary supplement formulations and license them to small manufacturing and retailing companies. They are authors of four books on aging and age-related diseases including the million plus copy #1 bestseller Life Extension, a Practical Scientific Approach (Warner Books, 1982). They have also published three other health books, two of which were bestsellers. Their fourth book, Freedom of Informed Choice: FDA vs. Nutrient Supplements, explained First Amendment free speech issues in relation to FDA regulation (prior restraints) of truthful, nonmisleading health claims for dietary supplements (for example, low dose aspirin and the reduction of risk of heart attack), focusing on the costs to the public health of such regulations and on alternative regulatory approaches.

1. In "IA, FDA's Policy Regarding International Standards,"

FDA says "...the agency's primary goal in participation in such standard-setting activities and use of resultant standards is to preserve and enhance its ability to accomplish FDA's public health mission, with the aim of enhancing regulatory effectiveness, providing more consumer protection with increasingly scarce government resources, and increasing worldwide consumer access to safe, effective, and high quality products."

COMMENT: Providing more consumer protection with increasingly scarce government resources cannot be interpreted to mean that the least expensive regulatory scheme to the FDA (eg., adopting the standards set by others) provides more consumer protection. The FDA is dealing with an increasingly information-rich environment. Attempting to reduce the complexity of this information by massive data deletion, eliminating of human variation by averaging, and oversimplification of current scientific understanding may be easy, it may be cheap, but it is not likely to enhance the public health. If the FDA does not have the resources to set standards itself, a quick and dirty "review" of internationally decreed standards by collecting public comments and "averaging" them (or, more likely, giving them arbitrary and capricious political weightings) is not a substitute. Such a process will result in a great public backlash against the FDA.

The FDA's most valuable, scarce, and fragile resource is legitimacy and public trust. If the FDA continues to lose this, large appropriations will not save the day. When the public looks upon the FDA's actions as politically motivated, arbitrary and capricious, and contrary to fact, FDA's health pronouncements will be widely ignored and scorned, and the FDA's credibility as a reliable source of health information lost.[1]

Also, in "IA, FDA's Policy Regarding International Standards," FDA notes that, in its Federal Register notice of Oct. 11, 1995 (60 FR 53078), FDA specified three considerations in the FDA's policy. Conspicuously absent from these

considerations was FDA encouragement of the provision of more truthful and nonmisleading information so that consumers can make informed choices. This is part of the Congressional mandate on the FDA under NLEA and DSHEA and must be taken into consideration as part of FDA's overall response to Codex.

2. In IB, International Agreements, FDA says "The U.S. Government is a party to a number of international trade agreements. FDA has participated in a number of recent international trade negotiations to ensure that under such agreements, FDA regulatory practices can remain focused on fulfilling the agency's mission to protect the public health while being supportive of emerging, broader U.S. Government trade obligations and policies."

COMMENT: If U.S. companies wish to meet internationally set standards so as to be able to market such "standardized" products in countries other than the United States, they ought to be free to do so. **But the products sold within the borders of the United States, as part of U.S. domestic trade, should not be required to meet international "standards."** Any products meeting Codex standards should, however, be allowed freely to enter the United States to be offered for sale in the U.S. and ought also to be legal to manufacture in the United States.

Harmonization of regulations is worthwhile in an economic sense until the opportunity costs of foregone choices are greater than the savings due to diminished regulatory costs. In a rapidly growing information-rich field, such as the relation between nutrition and disease, one must carefully consider the regulatory costs of foregone choices. The consumer will ultimately make this decision; the FDA can attempt to interfere, but in the long run the consumer -- not the U.S. government and not the FDA -- is sovereign in a market driven constitutional republic.

3. In the last paragraph under IB, FDA says: "Thus, FDA's

stated policy on international standards and the nation's obligations under the WTO provide compelling impetus for FDA to consider whether to revise its existing system for review and evaluation of international food standards, and if so, how such a revised system might be designed."

COMMENT: We believe that the FDA should not use its scarce resources to evaluate standards set by international bodies for the world at large which are not specific to the concerns of Americans and, which, at least in the case of dietary supplements, will result in even greater hostility toward the FDA and more legal actions taken against it. There are serious constitutional questions about the acceptance of standards set by an agency not a part of the U.S. government or employed by the U.S. government. This can be considered an unconstitutional redelegation of the authority delegated to the agency by Congress to set standards.[2] At the very least, for each standard the FDA will have to conduct its own full investigation, not just accept the conclusions of "expert" international committees, which is likely to be very costly. Moreover, the international committees, unlike U.S. government rulemaking bodies, are not required to conform to, for example, the First Amendment, the Commerce Clause, open meeting laws (Federal Advisory Committee Act), and the Administrative Procedure Act, which are other reasons to challenge any purported authority they have to establish standards for the commerce of United States citizens.

4. COMMENT: In order to accept Codex standards, it would be necessary to change DSHEA. While Codex defines dietary supplements narrowly as vitamins and minerals, the DSHEA defines dietary supplements much more broadly to include, in addition to vitamins and minerals, botanicals, amino acids, metabolites, food constituents, and others. Some substances that are regulated as dietary supplements in the U.S. under DSHEA are regulated as drugs in some Codex countries (for example, DHEA, a natural cholesterol metabolite found in the human body). In the United States, it is also possible for a substance to be regulated as

either a dietary supplement or a drug, depending upon whether it is intended to treat a disease (for example, beta carotene, when it is intended to treat xeroderma pigmentosum, is regulated as a drug). These are definitions and rules resulting from long political struggles in the United States to meet the desires of Americans. Neither the Codex nor the FDA can change the definition of dietary supplements in the DSHEA without Congressional passage of new authorizing legislation. As we (and, we believe, the majority of Supreme Court Justices) see it, a treaty cannot trump the United States Constitution, from which the federal government derives all of its authority. The federal government cannot legitimately give away the Constitutional rights of its citizens by treaty.

Major changes in DSHEA are not likely to pass this Congress; most current Members voted for DSHEA in the first place.

We propose, therefore, that companies wishing to export to countries requiring that their dietary supplements meet some international standard be free to meet that standard, but companies wishing to sell their dietary supplements within the United States not be required to meet these totally irrelevant (within the U.S.) standards.

5. COMMENT: "Under "IIB Role of Codex Standards Under the SPS and TBT Agreements of the WTO," FDA states that "The Conference also recommended that standards adopted include only those provisions necessary for consumer protection, particularly those related to health and food safety." As we and others have pointed out in other public comments to the FDA, there is a presumption of safety for foods and, under DSHEA, the FDA may not regulate dietary supplements more stringently than foods in common form. **In fact, an analysis of risks shows that foods in common form are far more hazardous than dietary supplements. Food poisoning alone kills over 9,000 people every year in the U.S.** This consideration should direct the allocation of FDA's scarce resources.

6. COMMENT: Under "IV. Request for Information. Part A," FDA requests responses to various questions. Part of the explanation of question #11 states that "...FDA believes that it will be faced with the following four situations with regard to standards that the agency believes to be suitable for FDA acceptance:" Situation #4 was given as: "(4) or the standard is not identical to or similar to any FDA regulation, and the adoption of the Codex standard is not subject to rulemaking under the act." We request FDA clarification as to how the FDA proposes to accept Codex standards without a rulemaking. We do not see how the FDA can avoid complying with the requirements of the Administrative Procedure Act, which provides the only way the general public can provide feedback to the agency concerning the regulations they must live with.

7. COMMENT: The last question given in this section ("IV. Request for Information. Part A") is: What goals, in addition to those listed previously, should be considered by the agency in developing any new regulations governing consideration of Codex standards? We believe that, in addition to the five other considerations FDA listed just before this question, there should be an additional consideration: (6) To ensure that the Codex standards do not conflict with the NLEA or DSHEA or the United States Constitution, including but not limited to the First Amendment protection of speech and press. We note here, for FDA consideration, that Justice Sandra Day O'Connor said, in an aside during a talk she gave that was televised on C-SPAN ("America and the Courts") on Sept. 27, 1997, that international agreements cannot take away property rights under the United States Constitution. We believe that the matter of the Constitutional limits on what the federal government can do through international agreements (eg. in expanding its powers under the Constitution or depriving its citizens of Constitutional rights) is about to become a major and highly contentious issue that will surely reach the Supreme Court.

8. COMMENT: Under "IV. Request for Information. Part B1," FDA proposes that, within an FDA notice of newly adopted Codex standards that FDA would publish in the Federal Register, FDA would describe the nature of the Codex standard, provide FDA's preliminary views on the standard, describe information the agency would need to evaluate the standard, invite public comment, and state the agency's preliminary plans to perform substantive review of the standard. We propose that FDA add the following to that information to be published in the Federal Register: (6) Identify conflicts with the NLEA, DSHEA, and the United States Constitution, including but not limited to the First Amendment protection of speech and press.

9. COMMENT: FDA asks, under "IV. Request for Information. Part B2, Enlisting Assistance of Expertise Outside of the FDA," what limitations there might be to the use by FDA of outside experts as part of an agency process established to review and evaluate Codex standards. One limitation would be that meetings of expert bodies working for the FDA would have to meet open meeting laws (the Federal Advisory Committee Act, FACA) and be open to the public. Some scientific experts may oppose this on the grounds that it will prevent "objectivity," that is, it would make transparent the wheeling and dealing and political tradeoffs that are an inherent and unavoidable part of any process, whether scientific or not, that is a part of political decisionmaking. However, since these decisions will affect hundreds of millions of people, there is simply no justification in an open society for making them behind closed doors. Indeed, FACA is the law, and legitimacy demands it.

10. COMMENT: FDA asks, under "IV. Request for Information. Part B3. Assessing Impact on Small Business," What issues, if any, would have a disproportionately large impact on small entities or would place small entities at a disadvantage relative

to large entities? Regulations, in general, impose a greater impact upon small companies, simply because the cost of regulation must be paid out of a much smaller financial base. Thus, the FDA should consider the impact of enforced Codex standards upon the dietary supplement industry, which is comprised of (mostly) small businesses. This problem would be entirely avoided if the FDA follows our proposal given above, that American companies wishing to offer products in other countries would have to meet whatever standards exist in those countries, but that Codex standards would not be mandatory within the borders of the United States.

11. COMMENT: Under "IV. Request for Information. Part C. Maintenance of Public File of FDA Determinations Regarding Codex Standards," FDA asks for suggestions. We request that FDA put all such information on the Internet.

[1] In the May 1995 FMI (Food Marketing Institute) survey, 45% of consumers trust no one and rely on **themselves** for assuring the nutritional value of the food they eat, up from 6% in 1994. Manufacturers followed at 23%, government 13%, food stores 5% and consumer groups 3%. A major shift has occurred at the expense of government, which led the list in 1990. In the 1995 survey, twice as many consumers reported looking to industry for assuring nutritious foods as the government. (as reported in Sloan and Stiedemann, "Guaranteed Success: How to Make Products Consumers Really Want," J. of Nutraceuticals, Functional & Medical Foods 1(1):69 (1997)

[2] See AFL-CIO v. Occupational Safety and Health Administration,

965 F.2d 962, 984 (11th Cir. 1992), as discussed in Martin et al, "Environmental Law: Determination on Silica May Expose Flaw in Rule," The Nat'l Law Journal pp. B12-B14 (March 17, 1997). This article is attached as Exhibit 1.

Submitted by,

Durk Pearson
Sandy Shaw
PO Box 2160
Tonopah, NV 89049

Sept. 30, 1997

RE:Docket No.95N-0304;Dietary Supplements Containing Ephedrine Alkaloids

DURK PEARSON & SANDY SHAW
Box 2160, Tonopah, NV 89049

TO: Dockets Management Branch (HFA-305)
Food and Drug Administration
12410 Parklawn Dr., Rm. 1-23
Rockville, MD 20857
Comments for Docket No. 95N-0304

Before the
FOOD AND DRUG ADMINISTRATION
Rockville, MD

In re: Proposed rule:	)	
Dietary Supplements Containing	)	
Ephedrine Alkaloids	)	Docket No. 95N-0304
Fed. Reg. 62(107): 30678-30724	)	
June 4, 1997	)	

18 August, 1997

INTRODUCTION TO COMMENTS OF DURK PEARSON & SANDY SHAW

Durk Pearson and Sandy Shaw are scientists and authors, maintaining residences in Nevada and California. Their three best-selling books include the million copy #1 best-seller Life Extension, a Practical Scientific Approach (Warner Books, 1982).

Their fourth book, Freedom of Informed Choice: FDA v. Nutrient Supplements argues that truthful, non-misleading speech on labels and in labeling is protected by the First Amendment against FDA censorship and discusses the cost to public health of such censorship.

Pearson and Shaw design dietary supplement formulations and

license them to small marketing and manufacturing companies. The formulations designed by Pearson and Shaw include dietary supplements containing ephedra herb. Pearson and Shaw and their licensed marketers and manufacturers (all are small businesses) would suffer substantial economic harm if the Proposed Rules regarding the use of ephedra herb in dietary supplements were adopted. Furthermore, Pearson & Shaw believe that consumers of ephedra herb dietary supplements would actually be endangered by the Proposed Rule.

Pearson & Shaw do not believe that the FDA has met their burden of proof under DSHEA that ephedra herb dietary supplements are unreasonably unsafe when used as directed; on the contrary, the evidence presented by the FDA shows that extant ephedra herb supplements with extant labeling are generally safer than food in common form. FDA's labeling proposals, moreover, are an impermissible prior restraint that violate the First Amendment of the U.S. Constitution. Pearson & Shaw request that FDA withdraw this Proposed Rule, attempt gather evidence that meets their DSHEA burden of proof, and if successful, reconvene the Committee, and develop a new Proposed Rule that, unlike the current Proposed Rule, is not arbitrary, capricious, contrary to fact, and does not violate the First Amendment. Please see Pearson & Shaw's 107 pages of Comments (attached).

Sincerely,

Durk Pearson

Sandy Shaw

Pearson & Shaw's Comments to the FDA on Ephedra Alkaloid Containing Dietary Supplements

All quotes, with page numbers given, are taken from the transcript of the August 27-28 1996 Food Advisory Committee meeting on ephedrine-alkaloid containing dietary supplements.

1. The FDA believes that ephedra contains ephedrine, a pharmacological agent, and is therefore a drug, not a food. As the FDA's Dr. Elizabeth Yetley said (Vol. I pg. 37): "Foods would be used for non-therapeutic purposes."

This is a very narrow view of foods. Many foods are used for therapeutic purposes, that is to treat or prevent disease, including garlic, fish oils, prunes, cranberry juice, low fat foods, yogurt, and vegetables and fruits. The FDA allows a health claim (may reduce the risk of cancer) for fruits and vegetables, as is also true for oat bran and wheat bran.

Dr. Hui: "It's very difficult to distinguish between what is a food and what is a drug. Think about glucose. Glucose is a drug when somebody is hypoglycemic and glucose is a deadly poison for someone who is very hyperglycemic." (Vol. I pg. 122)

Dr. Jasinski: "...I was curious in your definition of lack of pharmacologic effect as being a defining factor [of a food]. I have been drinking coffee, and I've got a tachycardia from drinking the coffee right now. So by your definition, coffee beans would not be allowed to be marketed because you can get a pharmacologic effect from coffee beans." (Vol. I pg. 124)

The notion that foods can be separated from drugs on the basis that drugs have a pharmacological effect and foods do not is false. At the most basic level, foods have a psychoactive effect by providing a sense of well being and energy following eating and the cascade of profound biochemical effects that result from eating, such as increase in blood glucose levels and alterations in release of neurotransmitters and hormones in various areas of the brain and body. Carbohydrates, for example, have been shown to increase the passage of the amino acid tryptophan across the blood-brain barrier into the brain, where

it is used by the brain in the manufacture of serotonin, a natural calming and sedating agent. Some people crave carbohydrates when anxious, thus using food as a tranquilizer, a pharmacological effect. It is well known that a few drops of sugar in water on the tongue of a crying infant often calms it; here sugar water is used as a medicine. This traditional infant tranquilizer is called a "sugar tit."

Many components of foods are known to have psychoactive effects and are consumed largely for those psychoactive effects, including coffee, tea, chocolate, and caffeine containing soft drinks. Recently, in fact, it has been discovered that anandamide (believed to be the natural ligand for brain cannabinoid receptors) and oleylethylamide, an inhibitor of anandamide hydrolase (the enzyme that breaks down anandamide) are found in chocolate, which may account for chocolate's production of a temporary sense of well being in many chocoholics. The expression "chocoholic" itself implies an intense craving and chocoholics often vie with each other over who has the most extreme chocolate craving. Paul Rozin of the University of Pennsylvania and his coworkers have found that 23% of premenopausal women crave chocolate in the perimenstruum, the days just before and after the start of menses. Those women also rate chocolate as being more pleasurable than other people do. These are pharmacological effects.

Tea (Camellia sinensis) is one of the most commonly consumed beverages in the world. In traditional Chinese medicine, tea is recognized to have various health and medicinal effects and is used as a treatment to help digestion, eliminate phlegm, diuresis, reduce sleeping time, improve eyesight, for detoxification, and to eliminate body heat (Han et al, "The Screening of Anticarcinogenic Ingredients in Tea-Polyphenols," Journal of Nutraceuticals, Functional & Medical Foods Vol. 1 No. 2, 1997, pg. 8). The health effects of tea are becoming known to growing numbers of Westerners as a result of the publication of papers in peer-reviewed scientific journals, which effects include antimicrobial, diuretic, antipyretic and immune function regulation, as well as possible preventive effects in

cardiovascular disease and cancer. Traditional Western use of tea was based on tea's tonic and diuretic effects. Indeed, the British **craving** for tea's stimulating effects was so strong that it led to a severe balance of trade deficit with China, which in turn resulted in the British opium war against China. Thus, tea is both a food and a medicine and has pharmacological effects.

Other foods consumed for psychoactive and pharmacological effects include beer and wine. Certainly some of the effects of these beverages are due to their alcohol content, but the same amount of alcohol ingested in the form of different alcoholic beverages provides a significantly different experience due to other active ingredients, such as the hops (an herb with stimulant/sedative effects) in beer and polyphenols in wines.

The distinction between foods and drugs cannot be made on the basis of the presence or absence of a pharmacological effect, particularly these days when the effects of individual components of foods are being isolated and foods created (for example, by genetic engineering) that contains larger or smaller amounts of selected components (for example, high oleic sunflower oil). We suggest that the only reasonable way to judge all foods and all drugs is on the basis of the ratio of risks to benefits of their use for individual users, not on the arbitrary and capricious basis of whether there is or is not a pharmacological effect.

Furthermore, there is an identifiable market of consumers who seek foods that enhance health, based upon such studies in the public domain as Wrick, Gilbert's HealthFocus study, Childs and Poryzees' survey, annual FMI consumer inquiries, and recent Yankelovich research (Childs, "Functional Foods and the Food Industry: Consumer, Economic and Product Development Issues," Journal of Nutraceutical, Functional & Medical Foods, Vol. 1 No. 2 1997, pg. 30). These individuals are comfortable with self-selection of products for health and subscribe to a health maintenance credo. Functional foods interests include disease prevention, disease therapy, performance enhancement, and (especially in the U.S.), weight loss. Wellness is in fact something of a personal philosophy or spiritual element to these consumers. Hence, the FDA must consider how FDA censorial or

prohibitive policies is going to be perceived by these consumers and, thus, the likelihood of such policies being effective for the intended purpose. It is exceedingly likely that the FDA's attempts to define foods as those substances that are only nutritive and not therapeutic is doomed to failure. Indeed, this was the message of the DSHEA. Because of this, FDA must withdraw the Rule, re-convene the Committee, reach a new conclusion that fits within the ambit of Congress's will, and re-propose a new Rule.

2. Individuals having heart attacks or strokes while using ephedra herb or ephedrine-containing products is not evidence that the ephedra herb or ephedrine-containing products caused the heart attacks or strokes. One thing we need to know is how many heart attacks and strokes would be expected in the user population during the period in question.

Mr. Ford: "...the figure that we have used is about a million and a half doses per day [of ephedra products], and that's just from the health food stores." (Vol. I pg. 250) Dennis Jones: "...the enormous number of users of this herb. My estimate is 5 to 8 million Americans each year for 10 to 12 weeks, but other people have four times that estimate." (Vol. I pg. 277) Dr. Bruce M. Chassy: I just wanted to make the point that if millions of people are taking products that contain ephedra alkaloids and we are seeing a very low incidence of these kinds of serious effects, **we need to know whether that incidence is any greater than spontaneously occurs**." (Vol. II pg. 118, emphasis added) Dr. E. Wayne Askew (Acting Chairman of the Committee): "And I don't think that we can give you an answer to that." (Vol. II pg. 119)

But information is available from a number of sources, including public agencies such as the Public Health Service and the Centers for Disease Control, for the heart attack incidence by age. The FDA did not provide this essential information to the Committee during their two day meeting in which they were evaluating the risks of ephedra alkaloid-containing products. How, then, could the FDA or the Committee members know whether

the incidence of the adverse events were greater for the user population than would have been expected of the general population in the users' age range?

Scientists at the FDA's Center for Drug Evaluation and Research make the same point in a letter to The Lancet (Vol. 350, July 5, 1997, pg. 69). In commenting on a study of the possible dangers of using non-sedating adrenergic agonist antihistamines, the scientists state: "...this type of analysis contains inherent flaws and may be subject to biases that could lead to misinterpretation of the data. First, this study does not account for the spontaneous rates of background cardiac events in the untreated population." These FDA scientists also caution that there may be a bias in reporting when there is heightened awareness of potential adverse events. The FDA has publicized its concerns about ephedra (see statement by Dr. Lori Love of the FDA, Vol. I pg. 198: "...we have publicized our safety concerns on ephedra-containing products a number of times."), thus creating a potential atmosphere of heightened concern and, hence, a possible reporting bias. They conclude their letter by noting: "...the FDA has been carefully monitoring spontaneous adverse drug reactions reported in association with the use of these antihistamines. This monitoring is not limited to analysis of crude reporting rates, but includes careful review of individual reports and follow up." We think that the evidence we present in these comments will show that the FDA has done nothing approaching a "careful review" and "follow up" in the case of adverse reports on ephedra alkaloid containing dietary supplements. This neglect supports the view of many that FDA has had a long-standing bias in favor of prescription and OTC drugs and against dietary supplements. Because of this, FDA must withdraw the Rule, re-convene the Committee, reach a new conclusion that corrects this error, and re-propose a new Rule.

3. FDA's treatment of the ephedra supplement adverse reaction reports exhibits FDA's infamous bias against dietary supplements. There have been thousands of complaints received by the FDA from users of aspartame (and MSG) claiming aspartame (or

MSG) caused adverse events, including seizures and strokes.

Strokes and seizures are "consistent" with the known effects of excess excitotoxic amino acid (e.g. aspartic and glutamic acids) activity, but that doesn't mean that aspartame (or MSG) caused them. FDA has consistently refused to reconsider the wide use of aspartame (and MSG) in foods (and in fact has increased the categories of foods that may contain aspartame) despite the large number of complaints because it is convinced by the scientific studies of aspartame (and MSG) that aspartame (and MSG) use is safe. However, safety trials of aspartame (and MSG) were done largely on normal people (some aspartame safety studies included individuals with phenylketonuria or non-insulin-dependent diabetes); none of the safety trials on normal individuals would be expected to include individuals with known cardiovascular disease, just as such individuals were excluded in the weight loss clinical trials with ephedrine. Hence, evidence for aspartame (and MSG) safety may be of no better quality than that for ephedrine, despite thousands of complaints to the FDA of adverse events, some of them serious. (For information on aspartame safety trials, see, for example, Stegink and Filer, Aspartame Physiology and Biochemistry, Marcel Dekker, 1984)

The association of the consumption of a substance and the occurrence of an adverse event is not the same as cause and effect. Dr. Cynthia T. Culmo, of the Texas Department of Health, discussed the state of Texas' recent experience with adverse event reports from users of ephedra-alkaloid containing products. The FDA has relied heavily on this evidence. However, note the exchange on Vol. I pp. 81-82 between Dr. Culmo and Dr. Jasinski:

Dr. Jasinski (Vol. I pg. 81): "But that's associated, and being causal and associated is different." "A certain percentage of young people are going to die from strokes or some unexplained cardiac event, and it's associated." "...have you done some sort of analysis on this data?"

Dr. Culmo (Vol. I pg. 82): "It's tabulated. It hasn't actually been broken down. But, again, we keep saying associated. I don't believe we've ever gone on record and said caused. (emphasis added) Here, Dr. Culmo backs down under the pressure

of tough comments and admits that these associations are just that, associations, and that, to her knowledge, the Texas Department of Health has never publicly called these associations a cause and effect relationship. Because of bias, FDA must withdraw the Rule, re-convene the Committee, reach a new conclusion that corrects this error, and re-propose a new Rule.

4. The FDA argues that even a clear warning will not protect all those in the sensitive population that should not use ephedra-alkaloid containing products because many of them may not know they have the medical conditions in the warning. However, this is a problem for all those sensitive to food components -- that they may not know they are sensitive.

Some food sensitivities, such as to peanut protein, can be fatal, while others can cause severe allergic reactions requiring hospitalization. People generally find out by eating the food and having a reaction. Most such food sensitivity discoveries probably occur in childhood. But this shows that warning labels only protects those who already know they are sensitive to a food, the same situation as exists with the ephedra herb warnings. FDA must withdraw the Rule, re-convene the Committee, reach a new conclusion that corrects this error, and re-propose a new Rule.

5. FDA instructed the Committee members not to consider any benefits of ephedra herb use. In the absence of benefits of use, this makes any risks totally unacceptable. However, there are benefits described by many users, benefits which consumers are capable of assessing, such as weight loss or energy. A number of peer-reviewed double-blind placebo controlled scientific studies have been published (and some of these cited during the Committee meeting) showing that ephedrine is thermogenic and can be used successfully to help in weight loss. This was one benefit that the FDA decreed could not be considered. Several committee members (1996) complained of the problem of considering safety when they were forbidden to consider benefits.

The FDA describes the Committee's conclusions on determining

a safe level (in the rulemaking proposal, pg. 29), "FDA notes that many members of the Food Advisory Committee stated that they were unaware of a basis for determining a safe level."

Dr. George Ricaurte (Vol. II pg. 222): "With the issue of a margin of safety, I'm left at somewhat of a loss because for a margin of safety you really have to have some indication and what I've heard this afternoon is that all purported purposes of use are being taken off the table [by the FDA] and it leaves you with, well, what the heck are we going to use this for. If there's no clear answer to that, then the margin of safety, quite frankly, has to go to infinity because **you can't do a risk/benefit when we don't have a perceived benefit.**" (emphasis added)

Dr. Inchiosa (Vol. II pg. 227): "...I could imagine this is going to be very confusing for the consumer, who look at a product that claims nothing, yet has a tremendous list of warnings because the warnings are going to be increased. And, so, really, in an age where we're trying to increase information it's disinformation or no information only a condition of more confusion." **"So, therefore, I agree with Dr. Ricaurte that since you have no claimed benefit, there's no margin of safety that can be calculated."** (emphasis added)

Dr. Croom (Vol I pg. 149) (comments directed to Dr. Yetley) "...as a scientist, when someone says no risk, I can imagine a spill of this water on this microphone, and when I come to one serious event and I get electrocuted." "Because no sounds more like why I go to church than a scientific analysis, okay?"

Because of FDA's incorrect charge to the Committee (that benefits could not be considered) the Committee's risk/benefit analysis could only consider risk, thereby resulting in arbitrary and capricious very low dose recommendations that are not in accord with the scientific evidence. Because of this, FDA must withdraw the Rule, re-convene the Committee, reach a new conclusion that corrects this error, and re-propose a new Rule.

6. Ephedra dietary supplements are already less dangerous than foods in common form. If you consider food poisoning as a

result of bacterial contamination alone, there are 9,000 deaths a year. This does not include the deaths, serious illnesses, and disabilities occurring in many more people from heart attacks and strokes resulting from food-derived excess calories, fat, and cholesterol. It is not uncommon for a heavy meal to trigger a heart attack in those at risk. The fat and the noradrenaline released in response to the food increase platelet aggregability, thus increasing the risk of an abnormal blood clot that can cause a heart attack or stroke.

People think food is much safer than it is and need to be educated so as to be more careful in using and preparing foods. This is education the FDA could be doing that would be a far better use of limited public funds than attacking the use of ephedra herb products on the basis of poor data.

John J. Guzewich (Vol. II pg. 238): "...if the CDC has a figure, you know, for infectious disease, which is my area, food-borne disease, that 20 to 30 percent of our population today is at risk for food-borne disease from infectious sources for high-risk population, I don't know if that is a fair number to say for these kinds of compounds [the ephedra alkaloids]."

Indeed, the CDC estimates that approximately 60,000,000 to 80,000,000 Americans suffer from food poisoning each year -- about one quarter to one third of all food consumers. How does the incidence of fatalities **caused** by bacterial food poisoning compare to the incidence of fatalities **associated** with ephedra dietary supplements? Nine thousand fatalities per year from bacterial food poisoning in the U.S. is equal to about one food poisoning fatality per 30,000 food consumers.

The FDA has found 21 deaths **associated** over three years with the use of ephedra supplements, or about 7 deaths per year. This is the associated-but-not-necessarily-causal numerator. What is the denominator, the number of people using ephedra supplements on any given day?

The members of the committee were very concerned that the FDA had not even attempted to supply the essential denominator information. The transcript of the 1996 Food Advisory Committee expressed grave concern about the FDA's lack of a denominator:

Dr. Hui, Vol. II pg. 61 "...what you have put together is very useful for us but these are literature written for professionals by scientists and it's used to treat diseases. There's nothing that's really safe. I think it's all risk-benefit ratio."

Right. That's why the denominator information is very important.

Mr. Appler, Vol. II pg. 81 "Your device center of FDA is having a conference on the 21st of September on a topic called Denominator Data. Since reports of injuries have to be filed under the statute for medical devices, the center is concerned that it can't evaluate the meaning of enumerator ... without knowing what the denominators are."

Dr. Ricaurte, Vol. II pg. 132 "I don't see Dr. Kessler organizing a meeting to address ephedrine OTC and convening an advisory group seeking advice as to what to do with regard to safety of these compounds, and yet here we are."
"Now the issue then is what is the denominator for--I mean, that's the only way I can try to get at that issue of safety as the agency seeks advice."

Dr. Jasinski, Vol. I pg. 161 "...yes, we have some serious events, but--I mean, we have a numerator but no denominator in any of this, and coming back to predict safety data, they're asking us to predict safety data without telling people to go out and do a clinical trial to validate the predictions."

Dr. Kessler, Vol. I pg. 161 "...I ask you to consider [giving] us your best judgment in light of what [data] exists."

The FDA expects magic, that scientists can make a scientific judgment affecting millions of Americans on the basis of very little and poor quality information provided by the FDA. The FDA has failed in its duty to provide necessary information, such as the <u>essential</u> denominator data, to the Committee, and should withdraw its proposed Rule until such time that it can hold a properly informed Committee meeting, which can then render an <u>informed</u> decision on which the FDA can base an <u>informed</u> Rule.

Dr. Marangell, Vol. II pg. 276 "We've been talking about the numerator and denominator, and in my assessment of this I

agree the data is very poor..."

Dickinson, Vol. I pg. 284 "Industry needs more information, needs to be able to come forward with more information on the denominators, as has been mentioned by several speakers here today."

Some denominator information was provided by industry during the committee meeting:

Mr. Betz, Vol. II pg. 27 "Over the past five years, Omnitrition has sold approximately 100 million servings of ephedra-based products. We believe that our position in the market is relatively small, probably around 5 percent of the market share. If you assume it's 10 percent, if you move out on a limb and assume it's 10 percent, that's over the last five years, one billion servings of ephedra-based products."

Dr. Ziment, Vol. II pg. 29 "Although you say one billion servings have been sold over five years, that means 200 million a year and I would guess that the average consumer takes what, 50 to 100 servings, which may mean one or two million people are taking this drug. Now, the real question for me is what percentage of one million people who take a drug should be allowed to have adverse reactions before control is taken?"

Mr. Betz, Vol. II pg. 30 "...our estimates, our understanding of the estimates with respect to the number of people in the United States who are actually using ephedra-based dietary supplements is ... more on the order of perhaps 10 to 20 million people, who have used at some point in the last five years ephedra-based supplements."

Mr. Ford, Vol. I pg 250: "...the figure that we have used is about a million and a half doses per day [of ephedra products], and that's just from the health food stores."

Dennis Jones, Vol. II pg. 277: "...the enormous number of users of this herb. My estimate is 5 to 8 million Americans each year for 10 to 12 weeks, but other people have four times that estimate."

Commenters Pearson and Shaw license a dietary supplement containing whole ground ephedra herb (about 1.8 gram of herb per serving, adjusted to contain 20 mg. total of ephedra alkaloids

per serving). Their experience in the market has led them to conclude that the number of consumers of ephedra alkaloid containing dietary supplements is similar to those given at the Committee meeting by representatives of the industry: 1,000,000 to 8,000,000 Americans consume these supplements on any day.

If as few as 212,000 people are using ephedra supplements and if the 21 deaths were actually a result of ingestion of ephedra alkaloid containing dietary supplements and if food poisoning were the only cause of deaths from consuming foods in common form, then there would be about the same incidence of deaths from consuming foods in common form as of ephedra alkaloid containing dietary supplements. In actuality, the number of people using these supplements is probably closer to ten times as high, there is no compelling evidence that the 21 deaths were all caused by the ingestion of ephedra alkaloid containing dietary supplements and, of course, there are many other causes (besides bacterial food poisoning) of deaths from consuming foods in common form.

Let us take the lowest industry estimate, 1,000,000 users on any given day, which would result in a worse case incidence estimate: 7 ephedra associated deaths per year per million ephedra users.

Compare this to 33 bacterial food poisoning caused deaths per year per million food users.

Even if all the deaths associated with ephedra were definitely caused by ephedra when used according to the label instructions (which the FDA certainly does not contend), the extant dietary supplements (some of which contain up to 110 mg. ephedrine and most of which also contain caffeine) with the extant labels (15 percent of which provide no warnings) are already 4 to 5 times safer than food in common form.

Moreover, remember that the food death incidence figure refers to bacterial food poisoning, not anaphylactic reactions, not cardiovascular deaths from excessive doses of calories, fat, and cholesterol, and not other causes.

Congress has **not** delegated authority to FDA under DSHEA to require dietary supplements to be safer than food in common form.

In this rulemaking, the FDA exceeds its Congressionally delegated authority by requiring a much higher standard of safety for dietary supplements than for food in common form. FDA's rulemaking is a clear expression of FDA's bias against dietary supplements. FDA must withdraw this proposed rulemaking because it is ultra vires and violates the APA.

The safest way to establish dose when using an ephedra alkaloid containing dietary supplement (or virtually any other kind of supplement) is to begin with a low dose (perhaps 1/4 to 1/2 of the suggested single serving size) and gradually increase the dose to the suggested level of use. As Adam Gissen noted on Vol. II pg. 38: "If you try to limit its [ephedra alkaloid containing dietary supplements] use, people are certainly not going to take something that you want to build up to the full dose over 10 days to two weeks, that's not possible to do in one week." FDA's proposed label statement limiting the dose and the use to one week will discourage consumers from building up the dose slowly. FDA must withdraw the Rule, re-convene the Committee, reach a new conclusion that corrects this error, and re-propose a new Rule.

7. Under DSHEA, FDA cannot regulate dietary supplements more stringently than foods in common form. FDA has done precisely this, hence it must withdraw the Rule, and re-convene the Committee with instructions to use a standard that does not fly in the face of the will of Congress.

8. FDA has not met its burden of proof, to show that ephedra is a significant and unreasonable risk when used according to label instructions, and not misused or abused. For example, FDA assumed consumers reporting adverse reactions were using the products according to label instructions. They must provide evidence for this, but did not attempt to do so. The FDA also admitted that it had obtained very few samples of what the consumer was using at the time of the incident in order to analyze them. Hence, they had no way to know whether those consumers for which adverse reports were made were following

label instructions or were abusing the supplements or even whether they were taking drugs such as cocaine at the same time. Dr. Lori Love (FDA), Vol. II pg. 149 "...we cannot verify in many cases what a consumer used."

Mr. Israelson, Vol. II pg. 119: "...on the formulas, which cause these serious adverse reactions at low dosage, 1-to-5 milligrams [of ephedra alkaloids], do you have the formulas themselves, so we could identify what else is in there?"

Dr. Lori Love, Vol. II pg. 119: "I do not have that in hand and we actually were just analyzing that data over the weekend."

Dr. Love, Vol. II pg. 107: "...we have only a relatively few samples where we've been able to collect the sample that the consumer was using at the time of the injury and be able to analyze that."

Dr. Georgitis, Vol. II pg. 107: "Dr. Love, I have a question for you, in terms of the serious adverse events below the median value of 20 milligrams per serving of the ephedrine alkaloids, do you have a percentage as to how many of those out of the total adverse events:

Dr. Love, Vol. II pg. 107: We haven't expressed our data in that form because, of course, we have only relatively few samples where we've been able to collect the sample that the consumer was using at the time of the injury and be able to analyze that." Because of this failure to meet the Congressionally mandated standard of proof, FDA must withdraw the Rule, re-convene the Committee, reach a new conclusion that corrects this error, and re-propose a new Rule.

9. People who don't know they have one of the conditions given on ephedra herb labels as contraindications, conditions such as cardiovascular disease, hypertension, diabetes, etc., may still use ephedra herb. Some misuse due to ignorance, however, is unavoidable no matter what regulations you put in place and the same problem applies to many other common and widely available products. For example, people who are at risk of heart attack may buy a shovel and shovel snow, eat a high fat meal or engage in an intense exercise regimen, and drop dead. People who

don't know they have diabetes may chronically eat high sugar foods and damage themselves via hyperglycemic glycosylation and other mechanisms. People with one of the medical conditions as those given on a label for which an OTC should not be used (including ephedrine containing OTCs) may not realize they have one of those medical conditions. Perhaps a warning could be added: "If you are not sure whether you have one or more of these conditions, see a physician before using this product." However, the list of warnings can be made only so long without type so small you need a magnifying glass to read it.

There has to be some room for personal responsibility in the sale and use of any product. That is why we favor education rather than the FDA representing that they shield consumers from the need to consider risks. It is dangerous for consumers to believe that the FDA has done all their thinking for them, thus excusing them from taking responsibility for their actions.

10. The FDA at several points during the 1996 meeting of the Drug Advisory Committee told the participants to ignore the issue of adverse reactions associated with the use of ephedrine alkaloids in OTC drug products, which includes phenylpropanolamine (in OTC products for weight loss), pseudoephedrine, and ephedrine.

Dr. Harry H.S. Fong (Vol. I pg. 47): "Currently, pseudoephedrine and phenylpropanolamine are used in OTC. So, what would happen if ephedrine is banned from the OTC market? Would pseudoephedrine and phenylpropanolamine follow up in also being removed from the market? They are, after all, similar alkaloids, and they are also derived from ephedra?"

Dr. Elizabeth Yetley (Vol. I pg. 47): "I think that what we're really focusing on today is not the drug issues, but the dietary supplement issues."

This response of Dr. Yetley of the FDA evades the important fact that anyone can walk into a supermarket or drug store and buy these OTC products containing ephedra alkaloids. If the FDA is going to restrict the dose or length of use of ephedrine containing products on the basis of safety, it is a reasonable

question why these others, with similar effects, would not also be restricted. (Note, too, that some OTC products contain 24 mg. of ephedrine plus 120 mg. of theophylline, a caffeine like drug. Moreover, the OTC pseudoephedrine and phenylpropanolamine containing products contain about 3 to 6 times as much of pseudoephedrine or phenylpropanolamine alkaloids as the total ephedra alkaloid content of a typical ephedra dietary supplement.) This again brings up the question of bias on the part of the FDA. Moreover, if ephedrine containing dietary supplements used for weight loss or energy have FDA set doses that do not provide the benefits sought by consumers, many such consumers may turn to available OTC products containing pseudoephedrine or phenylpropanolamine or ephedrine plus theophylline at higher dosages, with the perverse result that some consumers may end up using higher doses of ephedrine alkaloids than they did in the dietary supplements.

Dr. Irwin Ziment, Vol. II pg. 115: "...I feel that there is a disconnect in that we are hearing a lot about the dangers of ma huang and ephedrine without knowing the dangers of comparable orthodox drugs." Dr. Ziment, Vol. II pg. 116: "...Dr. Love, perhaps can give us a little bit more information on the side effects that are actually recorded, even on a year-to-year basis in adverse drug reports on the legitimate ephedrine products."

Dr. Lori Love (FDA), Vol. II pg. 116 "I don't have that data and I will defer to people from Drugs [FDA] on that." Unfortunately, there were no data on this essential subject supplied by Drugs (Branch of FDA) at the meeting.

There are political issues in whether the FDA regulates the OTC ephedra alkaloids or the ephedra alkaloid containing dietary supplements.

Dr. Jasinski (Vol. I pg. 99): "What I don't understand is if you look at the DAWN data that you quoted, pseudoephedrine was much greater a public health problem, two to three times by my estimate, as ephedrine, yet you control, you exempted pseudoephedrine when the DAWN data which was used for the basis shows it's two or three times the incidents and emergency rooms and deaths. Could you go through that?"

Frank Wickham (Texas Department of Health)(Vol. I pg. 99): "Yes, Dr. Jasinski, **that was a result of a political decision and based upon pressure brought upon the sponsor of the original legislation**." (emphasis added)

(Such political pressure can and will be brought to bear upon the FDA. Placing different standards upon the safety of ephedra alkaloids in OTC products and in DSHEA dietary supplement products would be arbitrary and capricious.)

Then, Dr. Jasinski said (Vol. I pg. 99): "...the health food stores make money selling ephedrine-containing products. The drug stores with the pharmacists make their money by selling pseudoephedrine-containing cold products, if you want to look at this cynically. Is this politics?"

Mr. Wickham, Vol. I pg. 100: "...I think that is part of the politics as far as the market is concerned, yes."

Here we see a clear conflict of interest between the marketers of ephedra alkaloid containing dietary supplements and the drug stores offering an ephedra alkaloid in OTC pseudoephedrine-containing cold products. We must carefully examine FDA policies to be sure that there is no FDA bias toward the OTC trade of ephedra alkaloid containing products. In the recent past the FDA has stated explicitly its concerns that the sale of dietary supplements might impinge upon the sales of pharmaceutical drugs.

FDA must withdraw the Rule and re-convene the Committee **without suppressing extremely relevant information**, make a new decision which considers this essential data, and issue a new rule.

11. Reducing the dose below an effective level (for weight loss or energy) will result in increased risks for those people who will take more to try to get the results they seek (not knowing how much they should take as one serving or the daily limits they should respect) and, perceiving the use instructions as "fake" or government propaganda, may also ignore the safety warnings, perceiving them to be equally "fake" or not useful as well.

Many consumers already using ephedra herb products will be familiar with doses above the dose suggested by FDA and may consider the entire label a misleading government message, with potentially lethal consequences, especially if the contraindications are perceived to be, like the dose and maximum use period disinformation, something to be ignored.

Setting dosages to arbitrarily low levels will not "fool" consumers and is not the answer to ignorance among consumers about safety considerations. Better education and more information is the best answer. It is not a perfect answer but, in a free society, it is far better than the alternative of FDA attempting to impose choices on millions of people. The FDA's credibility to dietary supplement consumers rests on whether consumers consider them a reliable source of information. If not, the FDA's "advice" will surely fall on deaf ears. Because of this, FDA must withdraw the Rule, re-convene the Committee, reach a new conclusion that corrects this error, and re-propose a new Rule.

12. Caffeine toxicity: Oral doses of greater than 1 gram of caffeine may be toxic in adults. That is about the same as is found in ten cups of coffee or in 10 No-Doz tablets. (Pentel, "Toxicity of Over-the-Counter Stimulants," JAMA 252:pg. 1902, 1984) The theophylline in OTC ephedrine products (120 mg. per tablet) is even more toxic in overdose than is caffeine. Because of this, FDA must withdraw the Rule, re-convene the Committee, reach a new conclusion that is free from arbitrary and capricious bias against dietary supplements and in favor of OTC drugs, and re-propose a new Rule.

13. We have examined published reports of adverse events with ephedrine, phenylpropanolamine, and pseudoephedrine that are exhibits to the FDA's proposed rulemaking, including 56, 60, 62, 63, 67, 68, 69, 70, 71, 73, 100, and 128.

We concluded that most of the adverse events were associated with abuse:

Reference 68 concerns a 28 year old woman with a three week

history of progressing shortness of breath, dry cough, fatigue, and orthopnea. She admitted to taking 25 mg. ephedrine tablets for 8 years to try to lose weight. One week before the onset of symptoms she reduced her daily intake from 80 tablets to 3 tablets, after which her symptoms rapidly worsened. 80 tablets of 25 mg. of ephedrine is 2000 mg. (!) a day. This is an immense overdose; it is possible that the tolerance experienced by users of ephedrine explains at least in part why this woman didn't die from taking so much.

Reference 67 concerns a 32 year old housewife who developed congestive heart failure after ten years of taking large quantities of ephedrine containing compounds for energy. It is not clear exactly what dose she was using but it appears to have been an immense overdose, as she was taking three bottles of an ephedrine containing cough medicine daily at the time of psychiatric referral.

Reference 66 concerns a 36 year old insurance agent who was taking a cough medication containing ephedrine. He had progressively increased his ephedrine intake until he was drinking more than a bottle a day, each of which contained 400 mg. of ephedrine.

Reference 69 concerned a 20 year old man who suffered an intracerebral hemorrhage after taking an unknown quantity of "speed," containing ephedrine. It was clearly used as a substitute for illicit drugs, such as amphetamine. The patient had used "speed" in the past but did not know the exact composition of the pills, though urine drug screen on admission revealed no amphetamine, methamphetamine, phenylpropanolamine, or caffeine.

Reference 70 concerned three case reports. Cases one and two had both used large quantities of the same ephedrine containing pills (each pill contained 15.3 mg. of ephedrine). Case 1 consumed 10 of the pills (150 mg. of ephedrine) all at once and Case 2 had consumed 10-20 of the pills (153 to 306 mg.) daily for 23 years! Case 3 suffered a ruptured berry aneurysm which, unfortunately for its victims, can result from many commonplace events, including exercise and emotional excitement.

Reference 86 concerned a 54 year old Polish woman who had become psychotic. She admitted under questioning to have taken increasing quantities of ephedrine over the past 20 years, to her most recent dosage of up to 15 tablets, each containing 30 mg. of ephedrine (450 mg. of ephedrine) five times a day (a total of 2,250 mg. of ephedrine!) during exacerbations of her asthma.

Reference 82 concerned a 26 year old man who developed psychosis. Three days before admission to the hospital, he started taking ephedrine (30 mg. five tablets twice a night) to keep awake while holding a job in a bakery. The total amount of ephedrine he had ingested in the three days before admission was 750 mg.

Reference 100 concerned a 45 year old man who had been taking a daily herbal diet supplement for weight loss. After several weeks of using "greater amounts," he began to get restless and couldn't sleep. At that time, he experienced personality changes and mania. The amount of ephedrine he was using is not clear, but the "greater amounts" suggests that it may have been an excessive amount and substantially greater than that recommended in the label instructions.

Reference 128 concerns a 33 year old woman who developed acute hepatitis in association with the use of ma huang. Unfortunately, this is not a problem uniquely associated with ma huang or even herbs in general. Any plant matter may have the problem. Ma huang from Asia may be grown in fields fertilized with fresh human feces. Commenters Pearson and Shaw (and many other dietary supplement formulators) require that the raw herb be sterilized with heat, ethylene oxide, or ionizing radiation before used in the manufacture of their licensed products. Most reputable herb suppliers do this before sale, even if it is not specified in the purchase order.

A number of Americans were recently reported in national newspapers as having developed hepatitis as a result of eating imported strawberries, causing something of a public relations problem at the FDA, since the public blamed the FDA for the problem.

Reference 56 concerns a 14 year old girl who took 15 to 18

capsules of a product containing (per tablet) 25 mg. of ephedrine, 200 mg. of caffeine, and 50 mg. of phenylpropanolamine, in a suicide gesture. She developed cardiac arrhythmias as a result, from which she recovered. If she took 15 capsules, her total dose was 375 mg. of ephedrine, 3000 mg. of caffeine (doses of caffeine alone of 1000 mg. or more may be toxic), and 750 mg. of phenylpropanolamine.

Reference 122 concerns potential risks to medically controlled hypertensive patients taking sustained-release pseudoephedrine for nasal congestion. The authors found that "pseudoephedrine administration did not result in statistically significant changes in any cardiovascular parameter. Mild disturbances in sleeping pattern and urinary retention in some male subjects were the only significant symptoms detected. The authors concluded that "while sustained release pseudoephedrine appears safe for the majority of medically controlled hypertensive patients without statistically significant effects on blood pressure or heart rates, our studies did show an upward trend in these parameters which, in a larger population of hypertensive patients, may prove to be clinically significant."

Reference 71 concerns a 17 year old girl who had made an attempt at self-poisoning 12 months previously but was said not to be a drug abuser. She was admitted to hospital after taking 20 tablets containing pseudoephedrine 60 mg. (a total of 1200 mg. of pseudoephedrine) and was diagnosed with an intracranial hemorrhage. The authors note at the end of the letter that "Pseudoephedrine has only rarely produced neurological complications. Because it is a very weak sympathomimetic amine, which has not achieved status as a drug of abuse or addiction. The present case, however, serves to illustrate its potential dangers." If ephedrine becomes available only in low dosages, pseudoephedrine might be abused more frequently.

Reference 62 concerns three patients that developed clinical evidence of heart injury after acute ingestion of phenylpropanolamine. The first case, a 24 year old woman had chest pains three hours after ingesting a single capsule containing 50 mg. of phenylpropanolamine, 4 mg. of

chlorpheniramine, and 0.2 mg. of belladonna alkaloids. It ought to be considered that the combination of these substances, rather than the phenylpropanolamine, was responsible for her injuries. Cases two and three were clearly cases of abuse. Patient two had taken eight capsules each containing 50 mg. of phenylpropanolamine, 8 mg. of chlorpheniramine, and 2.5 mg. of isopropamide. Patient three was a 31 year old schizophrenic woman who ingested approximately 40 tablets, each containing 50 mg. of phenylpropanolamine and 200 mg. of caffeine. This is clearly abuse.

Reference 63 concerns a 43 year old black woman who was brought to the hospital after two episodes of palpitations associated with shortness of breath, tinnitus, dizziness, diaphoresis, and inability to stand. She had no prior history of heart disease, but had a history of hypertension, which was controlled without medication. She was taking capsules that contained 75 mg. of phenylpropanolamine and 200 mg. of caffeine. The total amount she was taking was not specified. This woman should not have been taking a sympathomimetic with her history of hypertension.

Reference 65 concerns three patients. One, an 18 year old obese woman, was admitted to the hospital with neurological symptoms after taking two tablets of Comtrex^{R} for "congestion." The patient experienced a grand mal seizure at the hospital. No drug scan was done, so we do not know whether she might have been using any drugs along with the Comtrex. The second patient, a 26 year old man, drank three to six ounces of whiskey eight hours prior to admission. He had taken two black capsules three to four hours prior to admission. Each capsule contained 200 mg. of caffeine, 25 mg. of ephedrine, and 50 mg. of phenylpropanolamine. His blood alcohol was 5 mg% (5 times the legally drunk level). This man eventually died in the hospital. This combination of high dose alcohol, along with high doses of caffeine, ephedrine, and phenylpropanolamine is clearly drug abuse. The third patient was a 17 year old man who ingested two black capsules, later identified as "pick-me-up" capsules containing 200 mg. of caffeine, 200 mg. of ephedrine, and 50 mg. of

phenylpropanolamine. This man had a large stroke and died.

Reference 73 is a 1990 review of reported adverse drug reactions (ADRs) for phenylpropanolamine since 1965. "Since 1965, 142 ADRs have been reported in 85 studies, 69% of these in North America. Many such cases may go unrecognized. Of ADRs attributed to legitimately [OTC or prescription] sold PPA products, 85% occurred after consumption of OTC products versus only 15% after prescription drugs. The PPA product often contained combination ingredients, or PPA was consumed along with additional drugs. An overdose of PPA was taken in about a third of the cases. After ingestion of non-overdose amounts, 82% of the [reported] ADRs were severe. The most frequent side effects involved symptoms compatible with acute hypertension, with severe headache the most common complaint. Twenty-four intracranial hemorrhages, eight seizures, and eight deaths (mostly due to stroke) were associated with PPA ingestion." While the discussed adverse reactions are serious, 142 ADRs (though possibly underreported) should be compared to the tens of millions of consumers using PPA products during this 25 year period. In fact, this paper mentions that in 1981, a marketing research company reported that 9.5 million adults were using OTC diet aids, making PPA the fifth most used drug in the U.S. At the time of the publication of this paper (1990), three FDA advisory panels had judged PPA to be safe. In another study cited here, a review of over 200,000 prescriptions for PPA-containing products found no increased incidence of hospitalization for hypertension, arrhythmias, or stroke.

Reference 60 concerns a 28 year old man with no known cardiac risk factors and no history of smoking, drinking alcohol, or using reacreational drugs, or family history of heart disease, who had a heart attack after taking 60 mg. of pseudoephedrine. Subsequent examination showed that he had normal coronary arteries. The authors suggest that "pseudoephedrine, a sympathomimetic agent, may be implicated in the initiation of coronary spasm..." FDA must withdraw the Rule, re-convene the Committee, reach a new conclusion that corrects this lack of consideration for the information in the adverse reaction cases that FDA claims to depend upon, and re-propose a new Rule.

14. We have considered the data presented by the FDA in light of the paper on how to evaluate adverse drug reactions in Reference 43 (Jones, "Approaches to Evaluating Causation of Suspected Drug Reactions" in Strom, Velo (eds): Drug Epidemiology and Post-Marketing Surveillance, New York: Plenum Press, 1992, pp. 103-113:

The limitations of the FDA data make it very difficult to assess the degree of cause and effect versus mere association. For example, Table 3, the Naranjo Algorithm and Types of Data Requiring Judgement provides a series of 10 questions about the adverse event that can be used to assess cause and effect versus association. Question 5 is: "Are there alternative causes which could have caused event?" This question refers to confounders. For example, there is a background incidence of such events as heart attacks and strokes in the population of probably millions of individuals using the ephedra alkaloid containing products. The FDA did not provide information to the Food Advisory Committee on this background level of these types of events, making it virtually impossible to know whether the incidence of adverse events reported was higher or lower or about the same as the background incidence. As Dr. Bruce M. Chassy noted at the Food Advisory Committee meeting (Vol. II pg. 119): "...we need to know whether that incidence is any greater than spontaneously occurs." (Such data exist. For example, G. Michael Vincent, a cardiologist at the University of Utah School of Medicine in Salt Lake City says that there are 8,000 sudden, unexplained deaths among children and adults each year.)

The FDA has admitted that it has little information on what the consumer actually took. A consumer who is abusing a substance (by, for example, taking inappropriately large doses) may not be perfectly truthful about this stupid behavior when asked what they took. The FDA simply assumed that the consumer used the product according to the label instructions. For example, Dr. Love (Vol. I pg. 210) said "And the adverse events are reported when the product was **apparently** used according to label instructions, which **appears** to be in the majority of the

individuals where we have evaluable data." (emphasis added) Then on Vol. II pg. 120, Dr. Love says "Are you asking if we can verify that or any other information that our patients give us? I mean that's a very difficult question. If the patient told you that they took an over-the-counter product at X value [dosage], you would believe them."

There is a need to verify the dose the consumer claimed to take. However, Dr. Lori Love of the FDA noted (Vol. II pg. 149): "...we cannot verify in many cases what a consumer used." Then on pg. Vol. II 107, Dr. Love says "...we have only a relatively few samples where we've been able to collect the sample that the consumer was using at the time of the injury and be able to analyze that." Dr. Love admitted (Vol. II pg. 107) that the FDA could not provide information on the dose-response relationship (as, for example, how many of the adverse events took place at dosages below the median value of 20 milligrams per serving). This is important for answering question 8 of the Naranjo Algorithm: "Was reaction dose-related?" A median amount does not provide any information on the distribution of doses, eg., do the doses fall in a narrow range about the average or do they have a very broad range or is there a bimodal distribution. A small percentage of very high dosages could have had a large effect on the median. This is particularly important with respect to the deaths. Did they occur at especially high dose levels? It would have been much more useful if the FDA had supplied the average dose and the standard deviation.

Moreover, Dennis Jones reported to the committee (Vol. I pg. 275) that "...a fixed ephedrine/caffeine combination based mainly on the work by Astrup and his colleagues has been approved for weight loss indications in Europe and is being touted by many as the safest and most effective treatment available. Danish data indicated only 86 reportable adverse reactions, which were defined as reactions which necessitate stopping the therapy, out of 9.6 million daily doses during a two-year period..." The FDA should have followed up on this information before issuing their proposed new rules. We suspect that the FDA was in a big rush to get their rules out because of political, not scientific or

public health, considerations.

The FDA did not prepare a ma huang tea in the usual manner (heated in a pot) to determine how much of the ephedra alkaloids are extracted so as to know how much the consumer might have actually ingested in the case of ma huang products used as a traditional tea. Instead, the FDA put the ma huang into a pot and added methanol and water, boiled it, evaporated it, and put it on a carrier. That is not how a tea is prepared for human consumption! Plus you get much faster absorption when in the form of a concentrated extract on a carrier as compared to the absorption when a person swallows ground whole ephedra herb.

Question #4 of the Naranjo Algorithm asks: "Did reaction reappear when drug re-administered?" But Dr. Love (Vol. I pg. 202) stated at the Food Advisory Committee meeting that the FDA has reports on rechallenges in only 4 percent of the reported adverse events. FDA has done an extremely poor job of discriminating between causality and mere association without proof of causality, hence FDA must withdraw the Rule, re-convene the Committee, reach a new conclusion that corrects this error, and re-propose a new Rule.

15. The FDA seems to be in an awful rush to get these proposed rules issued, when the poor quality of the data available at the Drug Advisory Committee meeting would strongly suggest the collection of additional information, as we have suggested in these comments.

For example, on Vol. II pg. 158 Dr. Jasinski asks Dr. Love: "...have you prepared a report on your data, how you collected it, how you interpreted it and what conclusions you've made, and have you submitted this to internal review within the agency or outside the agency? And, similarly, have you taken the report from this ad hoc committee and submitted it to a peer review?" Dr. Love answered (Vol. II pg. 158): "We, of course, intend to do that, but we were analyzing this data even over the weekend to supply the information to you at this committee meeting here." **Then on Vol. II pg. 196, Dr. Kessler says "I have promised a number of people that the agency will work hard to get to a**

decision soon after this advisory committee." (emphasis added)

What about the report and the peer review that Dr. Love said the FDA "intend[s]" to do? That report and peer review were not a part of the record for public comment. Apparently, the FDA does not "intend" to do it. One suspects that at least some of the rush here is due to political considerations. FDA has behaved in a grossly arbitrary and capricious manner, using the Committee as little more than a fig leaf to cover their politically influenced decision. Perhaps now that David Kessler is no longer FDA Commissioner, FDA can take whatever amount of time is required to do the job correctly. FDA must withdraw the Rule, re-convene the Committee, reach a new conclusion that is based on science, not political considerations, and re-propose a new Rule. Congress, not FDA, is supposed to be the judge of political considerations.

Michael Davidson, M.D.
Analysis of Adverse Events Reports

16. There was inadequate time at the meeting to consider the report of Michael Davidson, M.D., a physician and fellow of the American College of Cardiology, assistant professor of medicine at Rush Presbyterian-St. Luke's Medical Center, and medical director of the Chicago Center for Clinical Research.

Dr. Davidson was commissioned by the NNFA to review the case files underlying 191 adverse event summaries (see Adverse Event Clinical Summaries at Tab F). He gave detailed analyses of all these events at the Food Advisory Committee meeting. Of the 191 events, he categorized 84 as serious. Of the 84 serious events, he determined that 13 were not related to ephedra, 8 were unknown for lack of information, 34 were remotely related, 22 were possibly related, and 7 were probably related. Dr. Davidson's report to the Committee is on Vol. I pp. 59-69 of the meeting transcripts. Unfortunately, he had only about five minutes to summarize his report. Then another 3 or 4 minutes were allowed for questions. The sort of careful, detailed breakdown done by Dr. Davidson ought to have been performed by the FDA, too, and also evaluated by an independent scientific group.

Michael Davidson, M.D. (Vol. I pg. 59):

Dr. Davidson's qualifications are cited above. In addition, the Chicago Center for Clinical Research, of which Dr. Davidson is the medical director, performs clinical trials for the food, drug, and nutritional products industries. Dr. Davidson states that he has over 10 years' experience as a principal investigator of more than 200 clinical trials in evaluating adverse reactions occurring during the trials. He was "retained by the National Nutritional Foods Association to review the adverse event reports received by the FDA on ephedra-containing products and to evaluate the recommendations of the dietary supplement trade associations and ascertain whether they are based on appropriate medical rationale."

Dr. Davidson (Vol. I pg. 60): "I evaluated the adverse event reports based on standard FDA criteria." "I have reviewed the Adverse Event Clinical Summaries found at Tab F of your [Committee members'] materials. In addition, I also reviewed the case files underlying 191 of these adverse event summaries. Of these 191 case files, I categorized 84 of the events to be serious and 107 not to be serious." "Of the 84 serious events, I found that 13 were not related to ephedra. I classified eight as unknown for lack of information. Thirty-four were remotely related; 22 were possibly related, and seven were probably related."

Dr. Davidson Vol. I pg. 61 "**Six deaths were possibly associated with ephedra. In two cases, not enough information was provided to consider an assessment. Two deaths were related to consumption of toxic doses of ephedra.**" (emphasis added) "Of the six deaths possibly associated with ephedra, three were due to sudden death and cardiac abnormalities were present on autopsy in all three individuals. Two of the possibly associated deaths were due to strokes. One of these deaths was due to a strong [error in transcription. This should be stroke] that occurred in an obese individual male who was using multiple other supplements and who had basilar artery atherosclerosis on autopsy. Another was a fatal stroke that occurred in a 44 year old female due to a left internal carotid artery occlusion. She had a very strong

family history of strokes. The sixth possibly associated individual whose death was from a seizure was also on phenteramine, Apidex, a prescription drug for weight loss. All of these six possibly associated deaths occurred on the high dose ephedra products."

"There were ten cases of non-fatal myocardial infarction. Of these ten cases, four, in my judgement, were not related to ephedra. In another three reports, there was not enough information provided to make an assessment. In three cases of myocardial infarction, a possible association with ephedra exists. In all three of these reports, post-myocardial infarction angiograms revealed normal coronary arteries. All three individuals were consuming high-dose ephedra in combination with caffeine."

"There were 17 reports of non-fatal strokes. Three cases were unrelated or remotely related to ephedra-containing products. In four additional cases, not enough information was available for me to make an evaluation. In the remaining ten cases, a possible association with ephedra products exists."

"In four of the ten possibly associated cases, these individuals had significant hypertension of hyperlipidemia diagnosed prior to the stroke. One case involved a male with a dilated left ventricle as a possible source of emboli. The remaining five cases involve premenopausal women. At least two of these women were on oral contraceptives. One of these was noted to be a cigarette smoker and the other was diagnosed as having a positive lupus inhibitor. In the three remaining possibly associated cases, oral contraceptive use is unknown and one was a cigarette smoker, and one of these women was on the product for over a year before she suffered as intracerebral hemorrhage. All but one of these stroke patients--the exception being the woman with a positive lupus inhibitor--were on the high-dose ephedra containing products."

"There were 16 reports of seizures. Of these cases, the majority of seizures occurred in individuals with either a history of seizures or an abnormal EEG on follow-up. As I am not a neurologist, I made only a limited evaluation of these cases."

"In summary, with the exception of two cases of toxic exposure to ephedrine, there appears to be only infrequent possible associations of ephedra-containing products with severe adverse reactions. These infrequent possible associations are characterized by coronary or cerebral thrombosis and seizures."

"Of the 105 non-serious adverse events that I reviewed, these are characterized by increases in blood pressure, tachycardia, nervousness, and dizziness. These symptoms are expected potential side effects of ephedra-containing products. These side effects appear to be dose-related, occurring in greater frequency in the high-dose ephedra-containing products."

"To test the hypothesis that low-dose ephedra products below 15 mg. per dose, which is the recommended dose of the working panel, do not have a significant rate of adverse events, I reviewed the adverse events associated with the ephedra product containing less than 15 mg. per dose. These products account for over one-third of all the ephedra-containing products, but only approximately 7% of the adverse events. Of these 42 adverse events on low-dose products, there were only two serious events that were possibly related to the product. I mentioned one was the young woman who had a stroke who also had a positive lupus inhibitor, and the other was a 55 year old female who had a seizure."

"Based on my medical review of the ephedra adverse event reports, I have the following opinions:"

"Number one, last year's [1995] recommendation of the ephedra working group and those of the dietary supplement trade associations are appropriate. The two main issues that appear to affect adverse reactions are the dose of the ephedra and the quality assurance of the product."

"The proposal to lower the ephedra alkaloid content to 60 mg. per day with 15 mg. of ephedra per dose, expressed as ephedrine equivalents, provides a margin of safety based on the fact that the vast majority of both serious and non-serious adverse reactions occurred with products that exceeded these dosage thresholds."

"Improved good manufacturing practices and quality assurance

will provide dosing consistency within product batches. Because dosing consistency is important, I would add to the recommendation that products that can be easily mis-dosed not be permitted."

"The ephedra working group also recommended very appropriate warnings and labeling instructions. I would also include on the label cautions against the use by smokers, those taking oral contraceptives, and those with a history of cardiovascular or seizure disorders."

Dr. Davidson (Vol. I pg. 66): "In conclusion, I would be happy to discuss with Advisory Committee members and FDA officials my rationale with respect to the relationship between the ephedra products and the adverse events. Thank you."

From the transcript, it appears that only 3 or 4 minutes was allowed for questions to consider this very relevant and lengthy report. The brief discussion was a totally inadequate evaluation of the report and certainly discouraging to any future industry effort to commission such an analysis. The FDA ought to consider that industry is not going to expend the time, energy, and money to pay for such analyses if the FDA is going to treat them in this cavalier manner.

The failure of the FDA Committee to consider the full details of Dr. Davidson's analysis of Adverse Event Reports (but, instead, to allocate 3 or 4 minutes to that) before reaching their conclusion renders the conclusion arbitrary and capricious. This failure is particularly egregious considering the FDA's failure to produce and provide a report to the Committee on the same subject matter. Although FDA has promised to provide such a report at some indefinite time in the future, it has not provided this sort of analysis to the Committee in a timely manner. In the absence of the promised FDA analysis, Dr. Davidson's report is by default the only study presented to the Committee on which adverse reactions were distinguished as likely to have been causally related to ephedra or ephedrine (rather than merely associated without adequate reason for assigning causality), the dose / adverse response curves for ephedrine, ephedra herb, ephedrine plus caffeine, and ephedra herb plus caffeine, and the

time course for the development of adverse reactions.

FDA merely brushed Dr. Davidson's report off without providing any specific criticisms of his methodology, without providing an alternative report to the Committee, and without permitting the Committee to either hear, read, or discuss his report before they were required to reach their conclusions. FDA's arbitrary and capricious treatment of Dr. Davidson's data and analysis requires that the Rule (which was made contrary to fact) be withdrawn and the Committee reconvened to give this very relevant and essential report actual consideration and debate.

FURTHER LEGAL CONSIDERATIONS

Food Advisory Committee meeting August 27-28, 1996

FDA LABELING AUTHORITY LIMITED

Vol. I pg. 12 James Prochnow, an attorney with Patton Boggs:
"...a dietary supplement manufacturer is able to inform each consumer of how a supplement or one of its ingredients affects the function and structure of the human body as long as it is not promoted to prevent, diagnose, mitigate or treat or cure a disease. As a result, a statement that a particular dietary supplement is effective for weight loss, mental alertness or clarity or for just plain energy does not make that related product a drug as defined by the Federal Food, Drug and Cosmetic Act."

FDA has no authority to prohibit labeling that refers to weight loss. FDA is violating the First Amendment prohibition against prior restraint. FDA is also attempting to manipulate peoples' actions by keeping them ignorant of these uses - uses that the FDA disapproves. As 44 Liquormart v. Rhode Island made clear, the First Amendment does not permit this, and any such attempt is subject to strict scrutiny.

IMPROPER STANDARD OF HARM

Vol. II pg. 96 FDA's Dr. Yetley:
"Can you identify a safe level in dietary supplements for a total ephedrine alkaloids per serving and per day as well as ephedrine itself? And how do you think we should deal with margin of safety issues? Can you identify questions of use for ephedrine alkaloids containing dietary supplements under which there is no risk of significant harm?"

Vol. I pg. 141 Dr. Yetley:

"We would ask that the committee first address the safety question from a perspective of can you identify a safe level of ephedrine alkaloids in dietary supplements for both the total ephedrine alkaloids that you find in the botanical sources, as well as ephedrine per se, and talk about that from both a per serving and a per day limit." "...what considerations are you taking into account when you think about margin of safety." "The third question we're going to ask is: Can you identify conditions of use for ephedrine alkaloids containing dietary supplements under which there is no risk of significant harm? And we have suggested that the definition of significant harm means are there a large number of adverse effects or a serious adverse effect in at least one individual." "The fourth question is: Can you identify conditions of use that are associated with a risk of significant harm, including levels and frequency of use above which there is a risk of significant harm?" (emphasis added)

"Assuming that after you give full consideration to this question and assuming that you come to the same conclusion that the working group did that there are probably safe conditions of use, then we will probably ask you to look at additional questions..." (emphasis added)

FDA's Yetley gives the Committee improper instructions. These instructions are ultra vires; they are a very substantial departure from the authority delegated to FDA by Congress, which is quoted immediately below:

Vol. II pg. 13 Mr. Prochnow:
Here he discusses the adulteration or safety provisions of the Dietary Supplement Health and Education Act, noting the section on Safety of Dietary Supplements and **Burden of Proof on the FDA**. "Section 402 of the Federal Food, Drug and Cosmetic Act was amended by DSHEA by adding a new subpart (f)(1) to (20). There, the Congress explicitly stated that a dietary supplement will be deemed to be adulterated only if one or more of four tests are proven by the FDA. This is the Congress talking..." "The three main ones are this: A dietary supplement is only unsafe or adulterated if it presents a significant or unreasonable risk

under conditions of use suggested in the label. Secondly, if the Secretary of HHS, not the FDA, declares that ingredient--since it's an ephedrine alkaloid--to be an imminent hazard to the public health or safety. And, thirdly, whether it is poisonous or deleterious."

"...the crucible of litigation [in the Formula One lawsuits] is revealing a lot of important facts because it is only there, where the full medical records of people are disclosed, when Formula One and other dietary supplements were ingested and related to the purported causes for things. Guilt by association is not enough in a court of law and should be not enough for this committee."

Vol. I pg. 145 Mr. Israelson:
"... the standard you are asking us to look at is significant harm, which has two sub-definitions, I'm just curious how you arrived at that definition, specifically in its two subparts, which is different from the statutory definition within the law." (emphasis added)

Vol. I pg. 145 Dr. Yetley:
"We really wanted this to be a scientific issue. We assume that FDA, as it goes to implement whatever recommendations come out of an advisory committee, will deal with it in the legal context."

Note that Dr. Yetley neither answers the questions nor corrects the false harm standard that the FDA ordered the Committee to use. Since the conclusions of the Committee were predicated on Yetley's false statement of Congress's harm standard, the Committee's recommendations must be set aside and the work redone ab initio by a Committee charged with the harm standard mandated by Congress's statute, not a different standard preferred by FDA.

Vol. II pg. 220 Dr. Fong:
"I have a serious problem with the last phrase [in question 3 put to the committee], 'of significant harm,' 'serious adverse effect

in at least one individual.' My daughter, who is 28 years old now, but as a child had great difficulty drinking milk--so milk is a food; milk presented serious effect to my daughter, as well as other Chinese or Orientals."

Vol. II pg. 222 Dr. Ricaurte:
"With the issue of a margin of safety, I'm left at somewhat of a loss because for a margin of safety you really have to have some indication and what I've heard this afternoon is that all purported purposes of use are being taken off the table and it leaves you with, well, what the heck are we going to use this for. If there's no clear answer to that, then the margin of safety, quite frankly, has to go to infinity because you can't do a risk/benefit when we don't have a perceived benefit." (emphasis added)

The FDA has made this conclusion inevitable by **requiring that the committee disregard** any evidence concerning the efficacy of ephedra for those purposes for which it is being widely sold: energy and weight loss. When you cannot consider any benefit, then of course even small risks will seem unacceptable.

Vol. II pg. 222 Dr. Ricaurte:
"Question number 3 [the possibility 'of significant harm' and 'serious adverse effect in at least one individual']--I'm not sure that there's many compounds that can satisfy that requirement, so the answer is, no, I can't, but I'm not sure that it's entirely a fair question with regard to the ephedra alkaloid per se."

Vol. II pg. 224 Dr. Kessler:
"Can I just help so we don't get off the track on milk, please? Significant risk--MIs, seizures, death--I don't think the food supply has those kinds of products."

This is incorrect. People can and do die of anaphylactic shock from eating foods with certain allergens such as peanut protein. Nine thousand people a year die from food poisoning due to improper production, transport, storage and/or preparation of

food. People have MIs as a result of eating a heavy meal, especially one rich in fat (which increases platelet aggregation and, thus, the likelihood of a heart attack).

Vol. II pg. 238 Mr. Guzewich:
"...if the CDC has a figure, you know, for infectious disease, which is my area, food-borne disease, that 20 to 30 percent of our population today is at risk for food-borne disease from infectious sources for high-risk population, I don't know if that is a fair number to say for these kinds of compounds."

HARM FROM USE IN ACCORD WITH LABEL INSTRUCTIONS RATHER THAN HARM FROM ABUSE IS THE CONGRESSIONALLY MANDATED CRITERIA

Vol. II pg. 50 Stephen Shapiro of Bass and Ullman:
"...we must not lose sight of the possibility that the reported consumer injuries may be the result of misuse rather than correct use. Also, looking at emergency room statistics, ... the enormity of the reports of misuse of such products as aspirin, acetaminophen and ibuprofen should be of a far greater concern."

Vol. II pg. 51 Mr. Shapiro:
"The special working group of the Food Advisory Committee of the Food and Drug Administration met in 1995 and determined that at least many of these anecdotal reports of injury do not withstand scrutiny. The special working group concluded that ma huang products do not present a significant or unreasonable risk of harm when sold with conservative dosage limitations, accurate label information and adequate warnings."

Vol. II pg. 52 Mr. Shapiro:
"The Act [DSHEA], among other things, amended 21 U.S.C. Section 343, to add the following: "A dietary supplement shall not be deemed as branded [should be "misbranded"] solely because its label or labeling contains directions or conditions of use or

warnings." "Clearly it was contemplated [by Congress] that some dietary supplements could have potential side effects and that warning statements would be appropriate."

MOST PROBLEMS CAUSED BY PRODUCTS THAT ARE ALREADY ILLEGAL

Vol. I pg. 82 Mr. Gary Coody, senior pharmacist in "our division" of the Texas Department of Health:
"...over the more than 1,000 cases included the drug product also, and so probably about half are synthetic ephedrine drug product. But most of the food supplement products -- I don't have a percentage -- I would say it's 90 percent contained caffeine also. (emphasis added)

Vol. I pg. 104 Dr. Dentali:
"...as we're talking about products that contain ephedrine alkaloids, it's also important we keep in mind the distinction between products that are extracts and that are, again, appropriately a dietary supplement and those that are pure ephedrine, whatever the source, and that we're able to look at the adverse reactions in those cases and determine which ones are indeed a single, isolated, purified ingredient that would render those misbranded and others that are indeed herbal extracts."

Vol. I pg. 136 Dr. Dentali:
"...I'm wondering if you did an actual analysis of the products associated with these adverse events and were able to determine which of them, in fact, were dietary supplements, meaning herb or herb extract, and which were purified alkaloids."

Vol. I pg. 136 Dr. Culmo (Texas Department of Health):
"Some were analyzed, not all of them. And I don't -- do you recall the breakdown?" "Obviously the first one we can think of is Formula One." "It claimed to be ma huang extract, and actually, in the papers, it was admitted that synthetic was

added."

Vol. I pg. 137 Dr. Dentali:
"Quite possibly this is not a dietary supplement."

Vol. I pg. 137 Dr. Culmo:
"But it's labeled as such."

FDA already has the legal authority to remove products that contain synthetic ephedrine masquerading as ephedra from the market; these products are clearly misbranded. The parties that engage in such fraud are also the parties most likely to have excessively high doses (synthetic ephedrine is far cheaper than real ephedra extract) and other false labeling, and to have no or inadequate warnings. The FDA has made no attempt to deal with this fraud/misbranding problem; instead it chooses to exceed its congressionally delegated authority and propound unscientific, arbitrary, and capricious regulations that will harm both the honest product producers and their customers.

Vol. II pg. 286 Dr. Chassy:
"I think there's one specific thing the FDA really ought to be doing, and I think the industry probably really wants to do the same thing. ...and that is that anything out there that is adulterated with ephedrine as the hydrochloride or the sulfate ought to be tested for--a virtually impossible task at this point, I agree--by the FDA and ought to be culled from the market. It is adulterated and it is mislabeled and misbranded, and it only hurts the industry and that's why they would like to see that done... I would give that a very high priority..."

Vol. II pg. 288 Dr. Chassy:
"What the evidence indicates is that there is clearly a smoking gun, if in only a few cases... Those few cases were sufficient to say these were effects which we might understand in an over-the-counter preparation, we could probably understand in a traditional medicine preparation, but we cannot understand in a dietary supplement--neither understand nor accept."

Vol. II pg. 289 Dr. Chassy:
"...I think there's a problem with the clinical trial and the problem is the comparative safety of ephedra and ephedrine alkaloids means--and it's very clear that many people can take these products repeatedly without doing any damage. I mean, there are millions of people taking them. That means that in order to do a meaningful clinical study of the effect of taking these products on people, it would have to be enormous to get the statistical power to see the adverse effects...You cannot do that study; it is incredibly expensive."

ARBITRARY AND CAPRICIOUS FDA CONCEALMENT OF ADVERSE EFFECT DATA ON OTC PRODUCTS CONTAINING EPHEDRINE, PSEUDOEPHEDRINE, AND PHENYLPROPANOLAMINE, ALKALOIDS FOUND IN EPHEDRA HERB

Vol. I pg. 226 FDA's Dr. Love:
"Texas and Ohio's data includes OTC drug products. This database does not. Where we identify a product afterwards as an OTC drug, we get a label, we find out that it's a drug, it's taken out of our database..." (Emphasis added.)

So it is not possible to compare the rate of adverse reactions reported for the ephedrine, pseudoephedrine, and phenylpropanolamine (which are the principal active ingredients in ephedra herb) containing OTCs as compared to the reports for ephedra herb containing dietary supplements. FDA has wilfully removed OTC adverse reaction information from their database that is just as relevant to the Committee's charge as is the adverse reaction information on the ephedra supplements. In some respects, this OTC information that the FDA concealed from the Committee is better for determining safe dosage because it is less noisy; amounts per dose, instructions, and warnings are all

specified in FDA OTC monographs. FDA did not supply this important data on many ephedra dietary supplement adverse reaction reports. One concludes that FDA is exhibiting its infamous bias against dietary supplements and in favor of more tightly regulated drugs. FDA must withdraw its Rule and convene a new Committee that has access to all relevant information.

ADMISSION THAT FDA PROVIDED NO DATA ON NUMBER OF EPHEDRA SUPPLEMENT USERS AND THAT FDA ACCEPTS INDUSTRY FIGURES

Vol. I pg. 240 Dr. Ziment:
"...I've got a report here of a "PrimeTime Live" television interview in which the CEO of the Los Angeles company that manufactures Herbal Ecstasy said that his firm alone sold 15 million units of this product. The amount sold in this country must be absolutely enormous. Is there any further details or extrapolation from this type of information to guess what the market is?"

Vol. I pg. 240 FDA's Dr. Love:
"I think generally FDA do not have this data and will have to defer to industry."

FDA'S NARROW VIEW OF TRADITIONAL USES OF EPHEDRA

Vol. I pg. 75 Dr. Culmo:
"The most common traditional use for ma huang is to treat respiratory disorders. There is no evidence to show that it was prescribed or promoted for weight loss, athletic performance enhancement, stimulation, or euphoria, as is commonly practiced today."

This is incorrect. A Chinese law (over 2,000 years old) prohibits horse riders who are under the stimulating/euphoric

influence of ephedra herb tea from galloping their steeds through villages. This early DUI (driving under the influence) law shows that the Chinese have traditionally used (and sometimes misused) ephedra for more purposes than FDA and Dr. Culmo are aware of.

COMMITTEE MEETING AFFECTED BY POLITICS MORE THAN SCIENCE

Vol. II pg. 68 Dr. McCausland:
"What changes is compromise. The facts don't change."

Dr. McCausland is referring to the fact that the Committee's recommendations have changed drastically since the 1995 meeting without any significant changes in the scientific data. This is science filtered through political considerations, which is not science at all.

Vol. II pg. 221 Dr. Ricaurte:

"I think it's telling that just from October '95 until here we are 8, 9, 10 months later, we've already gone from an estimated safety level down 10-fold and I'm not quite sure on what basis we're doing that."

FDA ADOPTION OF CANADIAN STANDARDS VIOLATES APA, FACA, AND DELEGATION OF CONGRESSIONAL AUTHORITY DOCTRINE

The FDA proposes that a dietary supplement is adulterated if it contains 8 milligrams (mg.) or more of ephedrine alkaloids per serving or if its labeling suggests or recommends conditions of use that would result in intake of 8 mg. or more in a 6-hour period or a total daily intake of 24 mg. or more of ephedrine alkaloids and requires a label warning not to use the product for more than 7 days. **The transcript records of the 1996 Food Advisory Committee meeting showed no consensus for a limit on the daily dose of ephedrine alkaloid containing dietary supplements, which ranged from 0 mg. to 60 mg. of the alkaloids a day.**

The limit FDA now proposes is virtually the same limitation

on the dose and length of use of ephedrine containing ephedra dietary supplements as Canada has recently done for OTC nasal decongestants containing ephedrine: 6 to 8 mg. of ephedrine per single dose repeated three to four times daily, used for no longer than 7 days.

Dr. Micheline Ho, Chief of the Product Regulation Division, Bureau of Pharmaceutical Assessment, Vol. I pp. 106-122, appeared at the Food Advisory Committee meeting, but provided none of the data that led the Canadian government to decide on that dose. Her presentation, however, may have influenced the final determination by FDA of the dosage limitation proposed in the rulemaking. It also influenced some of the Committee members. For example:

Dr. Wang, Vol. II pg. 189, "...since in the OTC drugs ephedrine is allowed to consume, what, 150 milligrams per day on the sustained release product, maybe a 10-fold safety factor, **following the Canadian way**, is 15 milligrams per day for food, but again I am just pulling that as a figure." (emphasis added)

Mr. Israelson, Vol. II pg. 223, "So, with that reservation that we're making decisions based on crucial cases without adequate evidence, I would repeat that **the Canadian proposal** as it's being used there is a reasonable model to follow. And my understanding of that proposal is that it would be based on 6 to 8 milligrams of total alkaloids. That would give a daily value of 28 to 32 total alkaloids." (emphasis added)

Dr. Fukagawa, Vol. II pg. 198, "...I would concur with the **Canadian** experience in that the safe level in dietary supplements would be anywhere between zero to 3.1 milligrams per day of the ephedra alkaloids, and then one can make the calculations after that with respect to ephedrine in terms of per-serving and per-day recommendations." (emphasis added)

Mr. Israelson, Vol. II pg. 191, "**...if we look at the Canadian levels, which were 6 to 8 milligrams 4 times daily, or 24 to 32 milligrams**, without the addition of other stimulant materials and with good manufacturing practices, I think that that's something that the industry would be able and willing to support and comply with." (emphasis added)

Mr. Israelson, Vol. II pg. 193, "Under DSHEA, we're able to have a lot of **labeling that would essentially follow what the Canadian labeling** would say, if that would be helpful to solve your concern." (emphasis added)

The data used by the Canadian government to determine the dose and length of use were not presented at the Food Advisory Committee meetings of 1995 or 1996, nor were these data available for American public examination and comment. The data that were presented at the 1995 and 1996 Food Advisory Committee meetings provided no or very weak evidence to support the Canadian dose and length of use limits. There was no Committee consensus on the dosage or duration of use limitations, yet the Canadian standard was chosen, perhaps because it was (relatively) politically safe and because Mr. Israelson, representing certain industry interests, urged the FDA to accept those limitations.

Per the APA (Administrative Procedures Act), the Canadian standard cannot be adopted without examining the data used to establish this standard, putting these data into the public record, and permitting public comment on the data, the basis for how the standard was established.

Under the APA, the ultimate regulation may remain controversial but at least the procedure ensures public access to the debate and identification of important issues and scientific evidence used in the agency's decisionmaking process. If the FDA accepts the Canadian government's conclusion without further examination and critical analysis, the FDA will have bypassed the salutary purposes of notice-and-comment rulemaking.

The adoption of another government's determination that is made without meetings open to the American public for examining the data underlying the determination are a violation of FACA (Federal Advisory Committee Act).

Moreover, the Congress has delegated to the FDA the authority to make determinations on safety issues concerning dietary supplements. It did not and cannot delegate this

authority to the Canadian government. The FDA does not have the constitutional authority to redelegate the rulemaking authority given them by Congress to the Canadian or any other extragovernmental entity. Hence, the use of the Canadian standard is unconstitutional. This same issue was part of a 1992 decision by the 11th U.S. Circuit Court of Appeals in which the court considered the propriety of OSHA's incorporation of the standards and findings of outside organizations (e.g., not part of OSHA, not part of the United States government and not subject to U.S. law concerning open meetings, etc.). In that case, the court vacated a "generic" OSHA rulemaking to set permissible exposure limits for 428 substances identified by the agency as air contaminants. The court found that while OSHA may "rely on the recommendations and documentation" of outside organizations (such as the 'threshold limit values' established by the American Conference of Governmental Industrial Hygienists), the outside body's findings "did not relieve OSHA of the responsibility for making detailed findings, with adequate explanations, for all statutory criteria. (See AFL-CIO v. Occupational Safety and Health Administration. 965 F.2d 962, 984 (11th Cir. 1992)

LABELING OF EPHEDRA DIETARY SUPPLEMENTS

FDA's Labeling Power Is Limited

"[N]o one disputes the proposition that [t]he Constitution created a Federal Government of limited powers") (New York v. United States, 505 U.S. ___,___(1992) (slip op., at 7) quoting [several citations deleted]. The powers granted under the Constitution to the federal government are outlined in the Constitution (the enumerated powers) and interpreted by the U.S. Supreme Court. The Bill of Rights describes further limits to the powers of the federal government.

The First Amendment of the US Constitution absolutely prohibits the FDA from banning labeling that is neither misleading nor deceptive. Indeed, Pearson & Shaw, et. al, have a First Amendment lawsuit against the FDA Commissioner before the U.S. District Court for the District of D.C. at this very moment. (Civil Action No. 95-1865 (EGS), District Court for the District of Columbia) If the FDA proceeds with its proposed Rule, it is asking for another lawsuit.

The Commissioner of the U.S. Food and Drug Administration promises, in his oath of office, to "protect, defend, and uphold" the U.S. Constitution. Unless we are to suppose that the oath of office is simply a ritual devoid of meaning and that the taking of the oath incurs no obligations, then the FDA Commissioner is obligated to seriously consider the constitutionality of his rules before it proposes them. There can be no excuse that it is somebody else's responsibility.

The U.S. Supreme Court has made it clear that the First Amendment does not permit government to keep information from the public in order to manipulate public choices. That includes, for example, information on the published peer reviewed clinical trials of ephedrine as a weight loss aid. It also includes information on the adverse effects reports received by the FDA

from consumers using OTC products containing the same alkaloids as in ephedra: ephedrine, pseudoephedrine, and phenylpropanolamine (which is racemic norephedrine, the principal metabolite of ephedrine in humans.)

If there are political factors involved in the FDA's decisionmaking, then the public has a right to know what they are. Though the disclosure of this information may be deemed an embarrassment or inconvenient to the agency, the Constitution trumps the agency's embarrassment or inconvenience.

Quotes from the U.S. Supreme Court decision in 44 Liquormart v. Rhode Island (1996 WL 241709 (U.S.))

"...a State's paternalistic assumption that the public will use truthful, nonmisleading commercial information unwisely cannot justify a decision to suppress it." (at 8)

"It is precisely this kind of choice, between the dangers of suppressing information, and the dangers of its misuse if it is freely available, that the First Amendment makes for us." (quoting from Pittsburgh Press Co. v. Pittsburgh Comm'n on Human Relations, 413 U.S. 376, 93 S.Ct. 2553, 37 L.Ed.2d. 770 (1973)

"In case after case following Virginia Pharmacy Bd., the Court, and individual Members of the Court, have continued to stress the importance of ... the impropriety of manipulating consumer choices or public opinion through the suppression of accurate 'commercial' information..." (J. Thomas, concurring, at 21)

QUOTES FROM COMMITTEE TRANSCRIPTS
AND COMMENTS
Food Advisory Committee Meeting
August 27-28, 1996

Vol. II pg. 12 James Prochnow, an attorney with Patton Boggs
"...a dietary supplement manufacturer is able to inform each consumer of how a supplement or one of its ingredients affects the function and structure of the human body as long as it is not promoted to prevent, diagnose, mitigate or treat or cure a

disease. As a result, a statement that a particular dietary supplement is effective for weight loss, mental alertness or clarity or for just plain energy does not make that related product a drug as defined by the Federal Food, Drug and Cosmetic Act."

Vol. II pg. 262 Dr. Ricaurte
"...I'm surprised at the fact that a number of potential uses and why these compounds, products, have been distributed have been taken off the table..."

It's no surprise. The FDA has instructed the Committee members that no use benefits may be considered in evaluating the risk/benefit of ephedra use, which requires that any mention of uses be eliminated. Prohibiting label mention of uses is unconstitutional as well as being a gross disservice to the customer. Note that the most common uses are ones where the consumer is able to judge whether they are receiving the promised benefits: satisfaction or reduction of appetite, weight loss, mental alertness and energy. Note further, DSHEA does not give authority to FDA to exclude benefits of a supplement from their Committee considerations.

Double blind placebo controlled peer reviewed published studies of the safety and effectiveness of 20 mg. ephedrine three times per day (e.g., Astrup, et al) were referred to several times during the meeting. FDA is not ignorant of this. FDA even officially admits "Other actions of ephedrine include stimulation of oxygen uptake and thermogenesis (heat or energy production)." (page 15 of the proposed Rule notice.) FDA's prohibition on the consideration of any benefits from ephedra dietary supplements is yet another example of FDA's bias against nutrient supplements, and is arbitrary, capricious, and contrary to fact. FDA must withdraw the proposed Rule, re-convene the Committee, refrain from forbidding the members from considering all relevant facts, and develop a new rule.

Vol. I pg. 153 Dr. Ziment

"...the patients who are taking herbal medicines rather than the standard drug produced by an ethical pharmaceutical firm, that individual is looking for magic. And if somebody's looking for magic, they're not going to be bound down by scientific recommendations. So even if we limit the amount of ephedra alkaloids in the drug, a person who's looking for a particular effect is simply going to take enough of the drug to give them that effect." "I think we're really expecting some sort of scientific control over the way people exercise free behavior, and that's not going to be easy."

And its not constitutional, either.

Vol. II pg. 245 Dr. Benedict
"And the cat, frankly, is already out of the bag. We can remove all of the labels regarding weight loss and all of the other things and people are still going to know that this is something that they think will work."

The FDA has required this committee to disregard any evidence for efficacy of ephedra in weight loss and anything else, but they cannot prevent that information from reaching the public. When the public has information which they think the government (FDA) is trying to keep from them, their respect for the FDA as a source of information plummets until it is all but ignored.

"In the May 1995 FMI [Food Marketing Institute] survey, 45% of consumers trust no one and rely on **themselves** for assuring the nutritional value of the food they eat, up 6% from last year [1994]. Manufacturers followed at 23%, **government 13%**, food stores 5% and consumer groups fell dead last at 3%. **A major shift has occurred at the expense of government, which led the list five years ago [1990].** Today, twice as many look to industry as government for assuring nutritious foods." (data from Food Marketing Institute, 1995. Trends in the United States Consumer Attitudes and the Supermarket 1995, Washington, DC, p. 57, as quoted from pg. 69 of Sloan and Stiedemann, "Guaranteed Success: How to Make Products Consumers Really Want" in J. of

Nutraceuticals, Functional & Medical Foods (Haworth Press) Vol. 1 No. 1, 1997.) (emphasis added)

The authors report in the same article that they have recently conducted proprietary research to determine what motivates consumers to purchase products in health food stores. They found (pg. 72) that 62% purchase supplements to prevent disease; 54% for increased energy; 40% to improve fitness; 31% to increase alertness; 27% to reduce stress; 25% to treat medical problems; and 21% to fight depression. As the authors note, "...the diet and disease connection with supplements has come a long way in just a few short years."

It is clear, from the above, that the government has suffered a decline in the extent to which the public relies upon it for nutritional information. If the FDA continues its practice of attempting to mold consumer dietary supplement choices by limiting information (such as prohibiting uses on labels) or by providing disinformation (such as mandating bogus time limits for use), the government's public credibility will decline further until it will cease to be of any relevance whatever in the area of nutritional information. **The FDA's proposed Rule will cause great consumer harm because it will cause loss of credibility in all label warnings, not just FDA mandated bogus ones.** All this is in addition to the insurmountable constitutional problems posed by the FDA's proposed Rule.

Vol. II pg. 37 Adam Gissen
"...one of the most telling things has been the desire to limit the use of products like this to some duration of time. This is in spite of a complete lack of scientific information indicating that this makes the product safer or more effective."

"In fact, ...all of the studies that have been done on ephedra have been done over a duration significantly longer than one week."

Millions of people have used ephedra dietary supplements for periods of time far in excess of one week. FDA's proposed Rule requiring the label to state a one week limit on duration of use

will backfire in a very serious manner. A warning that 99% of the customers know is false or misleading will reduce the credibility of the real pharmacologically justified warnings (e.g., contraindications such as cardiac arrhythmias and hypertension) thereby making the FDA directly responsible for an increase in adverse reactions and deaths.

Vol. I pg. 42 Dr. Larsen
The working group "agreed that the ephedrine alkaloid limit should be below that for currently marketed OTC drugs, and label instructions should advise consumers that more frequent use or using more than instructed does not increase effectiveness."

This is patently false and will reduce consumer confidence in label warnings. Instructions ought to advise consumers that more frequent use or using more than instructed increases risk of adverse reactions, not the obviously bogus statement that it does not increase effectiveness. FDA seems to believe that dietary supplement consumers are all idiots. This is untrue; market surveys have repeatedly shown that dietary supplement customers average considerably above the general population in formal education and intelligence. The FDA's Rule mandates label disinformation, and serious adverse consequences will inevitably occur unless the proposed Rule is withdrawn, new Committee meetings held, and a modified scrupulously honest Rule subsequently re-issued.

Vol. 1 pg. 280 Dr. Jones
"Finally, if the above is not sufficient, one extra line on the label will certainly kill the herbal street drug look-alike market: Warning -- exceeding the maximum permitted intake may result in temporary impotence."
"Those who understand the roles of the catecholamines in mammalian physiology will appreciate the scientific rationale for this cautionary statement."

Dr. Jones is entirely correct. His statement is not a bogus warning; it is truthful, not misleading, useful, and likely to be very effective.

The FDA does have a constitutionally legitimate role in assuring that dietary supplements sold in interstate commerce have adequate warnings. No warnings or inadequate warnings were found on a disproportionate number of products associated with adverse reactions:

Vol. I pg. 31 Ms. Binzer
(From 1995 working group meeting): Approximately 15 percent of all the dietary supplements collected in the review did not bear warning statements of any kind; 85 percent of the dietary supplements bore warning statements ranging from very general states, such as "consult your physician before beginning any nutritional or exercise program" to more specific warning statements, which tended to include recommendations not to use the product if consumers suffers from various medical conditions, experiences certain adverse effects, is taking certain medications, or is under a certain age.

Vol. I pg. 91 Frank Wickham
"...we've had this death of this young man due to a toxic level of ephedrine, taking it, of course, not having any idea that the product was dangerous..." (emphasis added)

Apparently there were no warnings on the label. This is certainly a legitimate and useful area for FDA action -- so long as the FDA mandated warnings are truthful and not misleading, rather than the proposed disinformation which will reduce credibility of all label warnings to the consumer.

Vol. I pg. 121 Ms. Ho (Canadian official)
"Subsequently, perhaps due to misuse or the fact that as a food the product did not contain any of the warning statements present in drug labeling, and because consumers may have exceeded recommended usage directions, two serious adverse reactions were reported in 1993" "Although as in most cases of adverse event reporting cause-and-effect relationship are not firmly established..." (emphasis added)

On the basis of misuse and/or a lack of important warnings, Canada now disallows the inclusion of ephedra as a non-medicinal ingredient in traditional herbal remedies and its use as food is no longer permitted rather than mandating appropriate warning labels. Canada does not have a U.S. Constitution, DSHEA (Dietary Supplement Health and Education Act), a FACA (Federal Advisory Committee Act), nor an APA (Administrative Procedure Act) and hence can not be used as a model for FDA action.

Vol. I pg. 133 Dr. Chassy
"You seem to have set national policy in Canada, if I heard you correctly, on the basis of two serious cases, and this committee is being asked to address itself to the issue of association versus scientific evidence of causality that the ephedrine alkaloids cause serious consequences. Could you share with us those serious cases and how you reached the determination, which you obviously did, that there was a causal relationship?"

Vol. I pg. 133 Ms. Ho (Canadian government representative)
"I don't have a lot of details about the two cases. I know that one was related to cardiovascular effects in a middle-aged male, I think, with a predisposing heart condition. The other one was a teenager who abused the drug product." **"People were being told ignore label directions and, yes, do take ten tablets instead of two tablets today if you want the product to be effective or if you want to lose weight faster."** (emphasis added)

If the FDA limits dosage to the Canadian rule of 8 mg. ephedra alkaloids three times per day for a maximum of one week instead of the usual informal industry standard dose of 20 mg. ephedra alkaloids three times per day without time limit, the above is exactly what will happen in the U.S. The FDA's ill designed proposed Rule is about to destroy the integrity and credibility of the ephedra dietary supplement warning and instruction labels and thereby increase the incidence of adverse reactions. This is not a theory; it has already happened in Canada and FDA cannot plead ignorance of the consequences.

Vol. I pg. 157 Dr. David Kessler

"We have two very real cases that the medical examiners have at least associated with the use of the products, the compounds under discussion. We need to reduce those risks. You're never going to reduce it to zero. You're never going to have somebody not do something very stupid that you can't predict. You can't safeguard against everything in this world. But I am convinced that those two individuals died needlessly because the information wasn't communicated to them about the hazards associated with these products." (emphasis added)

Dr. Kessler is correct. However, he did not state here what the labels on these products actually say about doses and about warnings. Were there no or inadequate warnings on the labels or did the individuals misuse the products?

Vol. I pg. 169 Constance Hardy (referring to FDA's second market review in April 1966, which identified 125 different dietary supplement products containing ephedrine alkaloids, some being duplicates (not necessarily the same formulation) of products collected in the first market review)

"Product labels, however, did not necessarily specify the form of the botanical source of ephedrine alkaloids, that is, whether it was an extract, a concentrate, or raw herb." "In some cases where the ingredient was listed as ma huang or ephedra without any further clarifying terms such as an extract or a concentrate, the ephedrine analytical values found on the products were higher than could be expected for the range of ephedrine alkaloids known to be present in the natural herb."

Vol. I pg. 174 Hardy

"...26 products had no warning statements at all; a general statement was noted on 14; disease or condition states were on 86 products; drug interaction statements were on 37; adverse effects noted were on 25 products; maximum daily use imperative--that's something to the effect 'Do not exceed'--you know, it specifically has the word 'exceed.' That was on 35 of the products, and age restrictions was 35."

Vol. I pg. 205 Dr. Love
Death of a 20 year old male college student who took eight tablets of an ephedra-containing "street drug alternative" although the label instructions were to take four and not to exceed four in a 24 hour period. The coroner's report stated (pg. 206) that the cause of death was "cardiac arrhythmia due to the synergistic effects of ephedrine, pseudoephedrine, phenylpropanolamine, and caffeine."

Dosage information was not given by Dr. Love; however, this is clearly a case of drug abuse, not use in accord with the label. We agree with FDA that labeling that promotes an ephedra dietary supplement as a street drug look-alike (e.g., Herbal Ecstasy) is false and misleading and can and should be prohibited in interstate commerce.

Vol. I pg. 275 Jones
"In the United States, our market surveillance covers over 300,000 users of ephedra herb with a particular range of products and has failed to reveal any serious adverse effects. We have had occasional minor complaints, but these were generally associated with failure to follow label instructions -- in other words, failing to start with a low intake and building up to a comfortable level...taking it too late and being kept awake at night--and these complaints did not occur in those who followed label instructions." "...the products concerned are manufactured under GMP conditions to a strict specification, and we analyzed both incoming raw materials and the finished product for ephedrine alkaloids and alkaloid pattern."

Vol. II pg. 37 Adam Gissen
"...these products have negative tolerance when looking at their effects on the central nervous system."

"And that's one of the things that makes something like ephedra a real poor alternative to speed. People develop tolerance, very very rapidly to the effects of ephedra on the central nervous system, especially used responsibly, in other

words, starting at a low dose and slowly building up to some recommended level."

Tolerance develops very rapidly to the cardiovascular effects of ephedrine, too. Several members of the Committee agreed that slowly increasing the dose over a few days would reduce the risks of adverse reactions. We agree with this, and believe that it should be part of the label instructions. Unfortunately, FDA's proposed rule requiring labeling to state a maximum use period of seven days makes that impossible, and hence this labeling requirement should be withdrawn. Instructions recommending a slow build-up to a full dose over a period of a few days to several days will reduce the adverse reactions far more effectively than a seven day limit which will be almost universally ignored.

Commenters Pearson & Shaw license formulations containing approximately 1.8 grams per dose of ground ephedra herb (the amount being adjusted on the basis of lot analyses to contain a total of 20 mg. of ephedra alkaloids). No ephedra extracts are used in this product, there is no caffeine or other methylxanthines, and it contains no synthetic ephedrine, pseudoephedrine, or phenylpropanolamine. Here are the label instructions:

"**DIRECTIONS:** Add 4 ounces of hot or cold water to one heaping tablespoon of mix. Stir briskly. Allow the mixed tea to stand for a couple of minutes. **DO NOT EXCEED THREE SERVINGS A DAY!** Keep in a cool, dry place. Keep lid tightly closed when not in use."
"**SUGGESTED USAGE:** For first three days, drink one serving in the morning as soon as you wake up. For the next three days, drink a second serving before lunch. From then on, drink a third serving one hour before dinner."

"**CAUTION: KEEP OUT OF REACH OF CHILDREN.** Not for use by children, pregnant or lactating women. May cause insomnia in sensitive individuals, especially if taken too soon before bedtime. Consult your physician if you are taking asthma medications, anorectic

(appetite suppressing) drugs, antidepressants, or cardiovascular medications. Do not consume this tea if you are pregnant or lactating or have high blood pressure, cardiovascular disease (especially cardiac arrhythmia), diabetes, prostatic hypertrophy, glaucoma (angle closure), hyperthyroidism, psychosis, thyroid disease, or Wilson's disease. Do not drink this tea within 14 days after taking MAO (monoamine oxidase) inhibitor drugs. If symptoms of allergy develop, discontinue use. Avoid the use of antacids containing aluminum with this product."

The label also discloses that the ingredients include ephedra herb powder. We wanted to put "contains 20 mg. ephedra alkaloids (primarily ephedrine)" on the label but were advised by one of our attorneys (who worked for the FDA for many years) that we should not do it because the FDA might use this statement as the basis for declaring our formulation to be a new unapproved drug. We believe that all ephedra herb containing products should disclose that information on the labels, stating the total amount per dose of ephedra alkaloids.

Note that these instructions increase the dose from the initial dose of 20. mg. ephedra alkaloids once per day to the final 20 mg. three times per day **over a period of seven days.** This very conservative rate of daily dose increase will be made unfeasible by the FDA's proposed rule mandating a labeled maximum use period of seven days; only one day of full dose and full effect would be allowed, hence rendering a product with these instructions ineffective and uncompetitive. For all practical purposes, the FDA may as well prohibit all labeling that instructs the customer to slowly increase their dose over a period of several days.

FDA has not met DSHEA's burden of proof for their requirement that the labeling limit use to seven days. A number of comments by Committee members and consultants also expressed doubts about the basis for such a limit. FDA's primary interest in the seven day limit appears to be their use of it to prohibit

any labeling which would suggest uses which would require longer than seven days. (See pg. 36 of the Proposed Rule notice, "a. Claims that promote long-term use.") FDA thereby attempts an end run around the First Amendment, believing that their seven day rule may receive more judicial leniency than the strict scrutiny that would apply to a prior restraint on such truthful non-misleading speech as labeling suggesting weight loss benefits when used for longer periods of time (eg. longer than a week).

In order to keep the label information-free regarding possible weight loss benefits, FDA ignores the increased risk to consumer safety. FDA is well aware that the development of tolerance to both the CNS and cardiovascular effects of ephedra alkaloids reduces the risk of these adverse reactions. They even admit this when they say on pg. 48 of the proposed Rule Notice, "FDA requests comments on whether the warning statement should disclose the possibility of increasing the risk of adverse events by a pattern of stopping and starting use." This is another iatrogenic risk created by the FDA's proposed 7 day use limit, which will cause those consumers who heed it to repeatedly start and stop taking the supplement.

FDA proposes to require that labels say "Taking more than the recommended serving may cause heart attack, stroke, seizure, or death." While it is true that taking too much of anything (including oxygen and water) can cause death, FDA has not met its DSHEA burden of proof that a warning of this severity is appropriate for their proposed label Rule specifying less than 8 mg. ephedra alkaloids three times a day for a week maximum. With such a low permitted dose, most consumers will continue to take more than 8 mg. TID, just as consumers have been doing for many years. Unfortunately, consumers won't get any information from labels on how much more it is reasonable to take. Those who take 2 to 3 times the label dose will be receiving about the same amount of ephedra alkaloids per dose that consumers have been taking for years. Those who know that the FDA has drastically

reduced the dose -- but not by exactly how much -- may take much more, thereby being subject to an increased risk of adverse reactions or even death.

The application of the FDA's above Rule warning to such a low dose (8 mg. TID) will be considered bogus by essentially all consumers who have previous experience with ephedra supplements, thereby casting unwarranted doubt on <u>real</u> and truly justified warnings such as "Don't take this product if you have hypertension or a cardiac arrhythmia." The FDA's above proposed warning would make much more sense if applied to a product containing 20 mg. of ephedra alkaloids or more, that is, if it applied to doses of the size of those that have been widely used for many years. There will be a serious cost involved if FDA requires the arbitrary and capricious use of inappropriately severe warnings -- a cost in **increased** adverse reactions and death due to loss of consumer confidence in fully justified warnings.

On page 47 of the 100 page proposed Rule notice, FDA proposes to require the statement "Larger quantities may not be more effective." As we have commented above, this is not only misleading (since larger quantities may also be more effective), it is so obviously deceptive (particularly with respect to the most common use, weight loss) that the credibility of all warnings on the label will be seriously reduced.

FDA then disinforms both the people of the United States and the Congress by saying "The agency is not aware of any data or other information that establishes that there are benefits from the use of dietary supplements containing ephedra alkaloids." (See pg. 47 of the proposed Rule Notice.) This is a lie. Ephedrine is the principal ephedra alkaloid. The transcripts of the meetings show that the FDA Committee is well aware of reputable peer reviewed published double blind placebo controlled clinical trials with ephedrine (though not necessarily on the same amount of the same compound when contained in the herb) that

show that it can be effective for weight loss. Indeed, (inconsistently) these studies are even discussed on pg. 17-19 of the proposed Rule Notice. An advertisement that was equally misleading would be illegal.

In any case, FDA's attempt to require more severe warnings on ephedra dietary supplement labels than on OTC (over the counter, no prescription required) drugs containing larger doses of the same alkaloids contained in ephedra supplements is arbitrary, capricious, contrary to reason, and is a further indication of FDA's bias against dietary supplements and in favor of more heavily regulated OTC drugs.

On pg. 51 of the proposed Rule Notice, FDA says:
"The agency considered the applicability of OTC drug data and tentatively concluded that these data, which involve use in a restricted population (physician-diagnosed mild asthmatics) under limited directions for use (i.e., not to exceed 12.5 to 25 mg. every 4 hours, not to exceed 150 mg. in 24 hours) and with warnings and contraindications for use, has no application here. The determination of safety for drugs is based on a weighing of the proven benefits of the use of the product against the risks. This approach may not be used with foods under section 402(a) of the act. The only question for food use under this section is whether it will cause harm or not. While the concept of "unreasonable risk" as stated in section 402(f)(1)(A) of the act, may imply that some evaluation of effects, including risks and benefits, is appropriate for dietary supplements, it is not necessary to reach that question here, because, as stated above, there are no demonstrated benefits for ephedrine alkaloids. Moreover, the risks attendant on consuming dietary supplements containing levels of ephedrine permitted in oral bronchodilator drugs (12.5 to 25 mg. ephedrine per dose) are manifest."

COMMENT: The FTC concludes "tentatively" that the OTC drug data on ephedra alkaloid containing products has no application here. The FDA argues that the OTC data apply to a restricted

population with directions for limited use and with warnings and contraindications. However, OTC drugs may be purchased freely by anyone (not just a restricted population) and used for any length of time and at any dosage their purchasers may choose. Adverse events resulting from abuse and improper use of the OTC drugs may provide valuable data for evaluating the adverse events resulting from the abuse and misuse of the dietary supplements containing ephedra alkaloids. We reviewed published reports of adverse events of individuals taking ephedrine, phenylpropanolamine, and pseudoephedrine containing products that are exhibits to the FDA's proposed rulemaking (exhibits 56, 60, 62, 63, 67, 68, 69, 70, 71, 73, 100, and 128). Our review indicates that most of the adverse events were a result of abuse or misuse of the products.

The FDA argues that the safety for drugs is based on a weighing of the proven benefits of the use of the product against the risks and that benefits may not be considered for foods, only whether they will cause harm or not. The FDA admits that the concept of "unreasonable risk" (as stated in section 402(f)(1)(A) of the act) may imply that "some evaluation of effects, including risks and benefits, is appropriate for dietary supplements, it is not necessary to reach that question here because...there are no demonstrated benefits for ephedrine alkaloids." There are a number of published peer-reviewed studies indicating that ephedrine has a thermogenic effect that helps with weight loss. But, in the final analysis, it is consumers using these dietary supplements who are the judge of whether they are getting benefits or not. In the case of weight loss or energy, a consumer is quite capable of evaluating whether he or she has lost weight or gained energy. If the FDA is going to assume that nothing has a "demonstrated" benefit other than those very few dietary supplements for which it has approved "health claims," then nearly all dietary supplements will be denied a risk/benefit analysis. This is unreasonable, arbitrary, and capricious.

The FDA then states that "the risks attendant on consuming dietary supplements containing levels of ephedrine permitted in oral bronchodilator drugs (12.5 to 25 mg. ephedrine per dose) are

manifest." A number of comments during the Food Advisory Committee meeting by consultants and Committee members who were experienced in their practices with the use of ephedrine for bronchodilation indicated that when used according to label instructions, these risks are not great. The real problem, with both OTC and dietary supplements containing ephedra alkaloids, is abuse and misuse by careless consumers.

AMOUNT OF EPHEDRA ALKALOIDS PER DOSE
AND TOTAL DOSE PER DAY

QUOTES FROM 1996 FOOD ADVISORY COMITTEE TRANSCRIPTS
AND COMMENTS

Although we have already made several comments as to why the FDA should not limit ephedra alkaloid to 8 mg. per dose with a total dose of 24 mg. per day, but instead should set the limit at 20 mg. per dose, 60 mg. per day, we hereby provide further reasons for this conclusion.

The most fundamental reason that the FDA has not met the DSHEA burden of proof on their dose limits is that **ephedra dietary supplements are already much safer than food in common form.** This is true even though the doses found in current products are given by the FDA as having a median of 17 mg. per dose with a mean of 30 mg. per dose (standard deviation = +-31 mg.). Unless FDA is allowed to set far higher standards of safety for dietary supplements than for food in common form (which is not allowed by DSHEA), a 20 mg. dose cannot be considered unreasonably unsafe when used as directed. We believe that a dose limit is needed (we consider a 110 mg. dose to be grossly irresponsible), and that 20 mg. total ephedra alkaloids per dose is reasonable as demonstrated by the current safety record. A 20 mg. per dose limit with a total dose of 60 mg. per day is realistic and will be accepted by consumers; the FDA's proposed limits will be generally ignored by consumers, thereby reducing the credibility of the other label warnings and instructions, and causing consumers to take multiple doses -- sometimes too many multiples -- thereby causing avoidable adverse reactions and harm.

Vol. I pg. 206 Dr. Love
In a summary of the FDA analyses on products associated with adverse event reports "where we had information on how the consumer used the product so that we could calculate the

milligrams per consumer use," the products range from one product at 0 all the way up to over 50. The mean dosage was approximately 30 mg. plus or minus 31. (!!) One of the supposedly ephedra-containing products associated with an adverse event had zero ephedra alkaloids in it. What were the rest of the ingredients?? FDA doesn't say.

Vol. II pg. 234 Dr. Askew
"From the information that has been presented to me, I've been impressed by the amount of people that are actually consuming this product without having adverse reactions, and I draw more my conclusions as to its relative safety from that than from the adverse incidence reports which are very difficult to deal with because of the nature of the reports."

Vol. I pg. 153 Dr. Ziment
"...the patients who are taking herbal medicines rather than the standard drug produced by an ethical pharmaceutical firm, that individual is looking for magic. And if somebody's looking for magic, they're not going to be bound down by scientific recommendations. So even if we limit the amount of ephedra alkaloids in the drug, a person who's looking for a particular effect is simply going to take enough of the drug to give them that effect." "I think we're really expecting some sort of scientific control over the way people exercise free behavior, and that's not going to be easy."

A second major reason why FDA cannot set their dose limits at 8 mg. per dose and 24 mg. per day is that **OTC drugs are readily available to anyone for any purpose at any supermarket that contain 24 mg. of ephedrine and 120 mg. of theophylline**, a caffeine like stimulant methylxanthine, with a 150 mg. per day of ephedrine label limit. FDA's Rule dose is not only arbitrarily and capriciously far lower, but it lacks reason; no increase in safety will occure if current ephedra supplement customers switch to an OTC product with higher doses of ephedrine

and methylxanthenes than the typical ephedra herb dietary supplement.

Vol. II pg. 104 Dr. Ziment
"If we say ma huang and ephedra products in dietary supplements are unacceptable does this create the concept that people who want to take these drugs have to buy orthodox ephedrine over-the-counter or would it give the message that we think people should go to MDs and have them evaluate the patient and then prescribe the ephedra products?" (emphasis added)

A third major reason that the FDA cannot impose the Rule doses is that **it is far lower than the doses traditionally used in ephedra herb teas.** FDA is legally required to allow the marketing of grandfathered products in traditional doses provided the labels are unchanged. It would be regrettable if FDA forced the industry to take this route because the original labels had few if any warnings and no drug interaction precautions. If this occurred, it would be harm caused by the FDA's proposed Rule, not harm inherent in the herb.

Vol. II pg. 105 Dr. Croom
"If you take the Chinese pharmacopeia the range of ma huang or ephedra that you can use is 1.5 to 9 grams. Actually most of the formulas used by practitioners that I've seen range around 6 grams but there is a ma huang tong that is based on a 9-gram dose." "If you take the more moderate, 5 to 6 grams, and you say the Japanese pharmacopeia is the only official source that sets a minimum, which is .6 percent, if you take in commerce, no matter what these range of values you've seen, the average is probably 1.2 percent. Then you will find that if you took 5 grams, which is approximately two tablespoons -- I have cut it and weighed it myself -- that you will find that at a .6 to a 1.2 that you are getting 15 to 30 milligrams per tablespoon in ma huang tea for the minimum concentration of .6 to an average of 1.2 If you take the two tablespoons, therefore, you are at the same dose that we

found most physicians using, between 25 and 50 for the pure compounds." (emphasis added)

The USP standard for ephedra herb is at least 1.2% ephedra alkaloids. Our own extensive experience is that most of the herb available on the US market is between 1.2 and 1.8%, in agreement with the observations of Dr. Croom.

Vol. II pg. 172 Dr. Croom
"The Chinese herb itself has between generally 1 and 2 percent [ephedrine alkaloids]. An average dose of the herb is 6 grams. That means you have between 6 and 12 milligrams of alkaloids there. So I'm taking traditional long-term use, what do we know from others, not to justify the use, but to say for safety where are the numbers..."

Incorrect math. The 6 grams of herb contains between 60 and 120 milligrams of alkaloids.

Vol. II pg. 219 Dr. Fong
Here, Dr. Fong states that the German Commission E dosage [no prescription required] is 1 to 6 grams per dose and that the "Japanese and the Chinese pharmacopeia of ephedrine alkaloid content in ephedra of 0.7 and 0.8 percent, not less than."

This calculates to a range of 7 milligrams to 48 milligrams a serving, though Dr. Fong refers only to the 7 milligrams. With a more likely ephedrine content, it calculates to 12 mg. to 72 mg. per dose.

Vol. I pg. 44 Ms. Bowen
"...we published a proposal in 1995 to remove ephedrine-containing products for bronchodilator use from the marketplace due to three events, one being diversion and difficulty containing that by the DEA under their current rulemakings, and also some evidence [emphasis added] in our adverse event reporting system of misuse of the products"

Removal was **not** proposed because after 50 years or so of use these products were suddenly found to be unreasonable unsafe when

used as directed. What evidence of misuse of products is in the adverse event reporting system? FDA deleted all OTC data from their database and refused to supply it to Committee members even though Committee members asked for it. Note, too, that while the FDA mentions this previously proposed (and failed) removal of the ephedrine alkaloid containing bronchodilators in the Rule Notice, FDA deceptively leaves the false impression that this previous proposed removal was for safety reasons, not because ephedrine was being diverted for use as a precursor of illicit blackmarket methamphetamine.

Vol. I pg. 45 Ms. Bowen
"over the counter bronchodilators has single dose of 12.5 to 25 mg. of ephedrine, not to exceed 150 mg. a day."

Primatene tablets, containing 24 mg. ephedrine plus 120 mg. theophylline, are still on the market. So are products containing pseudoephedrine (the second major ephedra alkaloid) and phenylpropanolamine (a racemic version of norephedrine, the principal human metaabolite of ephedrine. The maximum dose of OTC pseudoephedrine is 60 mg., and the maximum OTC dose of phenylpropanolamine is 120 mg.

Vol. I pg. 46 Dr. Jasinski (the drug abuse expert)
"Most of the concern of the DEA is not with ephedrine at a retail level."

Vol. I pg. 72 Dr. Askew
"Now, also the question has been raised as to whether or not the OTC drugs are experiencing the same incidence of adverse reaction reports as the food products are, and I think this is probably a fair question."

Vol. I pg. 73 Dr. Culmo
"TDH [Texas Dept. of Health] provided oral and written comments in October 1995 to the committee's working group on ma huang. At that time, we indicated that TDH had collected 900 reports of adverse reactions to ephedrine-containing products for Texas

citizens; that was 400 from over-the-counter or OTC drug products and 500 from food products. We now have substantially more than a thousand reports of injuries or adverse events." (emphasis added)

Vol. I pg. 162 Dr. Ziment (expert on the use of ephedrine in asthma and other respiratory diseases)
"As somebody who has been treating asthma for a long time, I regard ephedrine as an asthma drug. And I think I know that the dose is something between 50 and 60 mg. three or four times a day. And I rarely have changed those dosages in treating patients, whatever their underlying or secondary condition may be. So I think we should use those dosages as a starting dose of what is safe and reasonable, and make the equivalent dose of ma huang equated to those dosages of pure ephedrine." (emphasis added)

Vol. II pg. 165 Dr. Ziment
"...this implication that more than seven days could be hazardous, as opposed to less than seven days in some sort of long-term fashion. I just don't see the evidence for that."

Vol. II pg. 240 Dr. Katz
"When I looked at this question, I had to divorce my experience as a physician with ephedrine since as a practicing pediatric pulmonologist back in the late '70s and early '80s we used a lot of ephedrine for children with asthma. It has been supplanted by obviously much better drugs, but we saw very few serious adverse effects."

Vol. II pg. 105 Dr. Croom
"One of the things that we discussed in the committee [1995 working group] was certainly that when you set the level at 25 total ephedrine alkaloids, but ephedrine being seen as the most cardioactive and potentially the largest side effect being lower at 20, was one of the things that was discussed." "...there was

also consensus certainly between Dr. Tyler and I and this was also forwarded to the charman, that if things were used in combination with things like caffeine that we were both in agreement that ratio--this is individual dose--should be a 10/15 level, not a 20/25, because of what was unknown we felt like in the lack of data, even though there is some data." (emphasis added)

We agree with Dr. Croom and Dr. Tyler: 20 mg. ephedrine in 25 mg. total ephedra alkaloids per dose if there is no caffeine or other methylxanthines, 10/15 mg. per dose if the product contains caffeine or other methylxanthines, with a maximum of three doses per day.

Vol. II pg. 57 Gordon Peterson
"And I then decided I would look at what is considered the pharmacological bible, Goodman's and Gilman's, in their book, Pharmacological Basis of Therapeutics, and found ephedrine listed as follows and I quote: 'The usual oral dose is 25 to 50 milligrams repeated every three to four hours for a 150 to 300 milligrams per day dose.' "I then ... looked in the American Hospital Association's Hospital Formulary which recommends the following: 'The usual adult dosage is 25 to 50 milligrams every three to four hours.'" "Another quote from this American Hospital Association's Formulary is... 'For self medication in children 12 years old and older, the usual dosage is 12.5 to 25 milligrams every four hours.'" "It goes on....'For children 6 to 12 years of age, ephedrine is safe at 6.25 to 12.5 milligrams every four hours.'"

Vol. II pg. 58 Mr. Peterson
"Another study. This one comes from the International Journal of Obesity 1993, and I quote: 'We conclude that the ephedrine/caffeine combination is safe and effective in long-term treatment in improving and maintaining weight loss.'" "'The side effects are minor and transient and no clinically relevant withdrawal symptoms have been observed.'"

Vol. II pg. 75 Mr. Appler

"I find it difficult to believe on any scientific or toxicological basis that my ingestion by inhalation [sic, this should be per oral] in a health compromised population, 25 milligrams single dose, 150 a day, is safe as declared by FDA and its experts. But that oral ingestion at the levels you recommended last October [1995 working group] 20 milligrams of ephedrine alkaloids, 25 total alkaloids, AD/100 per day, is possibly the hazard that FDA has tried to present it as."

"If that were so, we would be seeing literally thousands of injuries among the tens of millions of daily users of bronchodilator products. Needless to say, despite the far more sophisticated system FDA has for capturing drug reactions, no such substantial reports for bronchodilator use have appeared."

Not only that, but Primatene tablets containing ephedrine are available OTC, meaning that anyone can walk into a supermarket or drug store and buy them and then use or misuse them any way they wish. If significant adverse reactions were occuring in users (rather than high dose abusers) of Primatene tablets, the lawsuits alone would have driven Primatene tablets off the market long ago.

Vol. II pg. 16 Mr. Prochnow

This testimony concerns an approved protocol for a clinical study of ephedrine: "The Institutional Review Boards of Harvard and Vanderbilt on a preliminary test they go through would not probably have approved the protocol for these studies unless they felt that there was a good possibility or probability that the levels of ephedrine that were going to be tested, about 25 milligrams per dosage... was an appropriate safe level. ... the parameters of the protocol included at least 30 milligrams of caffeine per serving size and at least 25 milligrams of ephedrine alkaloids per serving size."

Vol. II pg. 111 Dr. Ricaurte

"What I'm puzzled by is the apparent disconnect between the data on the products we've been discussing the last day and a half and

what several members of the committee has said is our 50-year long experience with OTC ephedrine-containing products." "...the issues of some of the adverse effects, certainly they haven't loomed as major concerns with OTC products contained in the ephedra alkaloids. Is it the reporting system? ...if we are going to use, as was suggested by the Special Working Group before [1995], as a benchmark or a starting point on dosage issues, prior experience with OTC products containing the ephedra alkaloids, then I think the issue of why the apparent disconnect exists is critical."

Vol. II pg. 111 Dr. Love
"Of course, the reporting systems are different and the products are very different."

The FDA is focusing on ephedrine and other ephedra alkaloids. Thus, it is reasonable to compare adverse reactions with other products containing ephedrine and other ephedra alkaloids. The admission by Dr. Love that the reporting systems are different may be pertinent in that there has been no FDA publicity concerning alleged dangers of the use of the OTC ephedrine, pseudoephedrine, and phenylpropanolamine products during the period when FDA has been publicizing the alleged dangers of dietary supplements containing those alkaloids.

Vol. II pg. 112 Dr. Love
"The product from one manufacturer containing ephedrine plus these other ingredients cannot be compared necessarily to a product from another manufacturer that may be listed as containing the same ingredients. You don't know what their source is, you don't know what their potency or anything else is. And because there can be natural variations, even the products from a single manufacturer can have lot-to-lot and batch-to-batch variability that may well affect their safety profile."

This is a good reason for doing a competent followup on reports of adverse reactions, to find out what the consumer actually ingested. The FDA cannot just say "we don't know anything so let's just ban all products containing ingredients

that may have (but we don't know) been involved."

Vol. II pg. 115 Dr. Ziment
"I want to follow-up what Dr. Ricaurte was referring to. I still don't feel that I understand what the reported and recognized dangers are of taking either over-the-counter ephedrine or even pseudoephedrine or phenylpropanolamine. And I certainly have prescribed agents of this nature. And I feel there is a disconnect in that we are hearing a lot about the dangers of ma huang and ephedrine without knowing the dangers of comparable orthodox drugs." (emphasis added)

Vol. II pg. 116 Dr. Ziment
"Well, Dr. Love, perhaps can give us a little bit more information on the side effects that are actually recorded, even on a year-to-year basis in adverse drug reports on the legitimate ephedrine products."

Vol. II pg. 116 Dr. Love
"I don't have that data and I will defer to people from Drugs on that." (emphasis added)

However, no people from Drugs appeared at this meeting to inform the committee members on these data. It is appalling that the FDA did not provide this clearly very relevant, very important information that is indispensable to making a scientific judgment on the risks in using products containing ephedrine alkaloids, particularly when this data was identified as important and requested by Committee members.

Vol. II pg. 116 Dr. Weintraub
"...there are no serious adverse effects within the dose range that is printed on the label. There are some adverse effects that occur due to taking of products with different names which may mislead the public or be sort of fanciful names that would indicate a different indication other than bronchial dilation. So, but, as bronchial dilator, used as a bronchodilator there are no major adverse effects." (emphasis added)

Vol. II pg. 134 Dr. Kessler
"...the question about safety that we're asking you today is safety in the context of a supplement to a diet. That's what we are asking you for. We are not asking you for safety in the context of an asthmatic."

But the data on the safety of ephedrine alkaloid containing OTCs are quite relevant to the interpretation of safety information on ephedrine-alkaloid-containing dietary supplements.

Vol. I pg. 67 Dr. Jasinski (a drug abuse expert)

"...if you looked at the data on phenylpropanolamine, it looks exactly the same." "...death as a result of effects on the cardiovascular system are very rare even for amphetamines...most deaths with essentially sympathomimetic amines with the amphetamines which result in their control as a result of intravenous abuse and infections causing death."

Vol. I pg. 68 Dr. Davidson
"...if the products contain less than a certain amount, the incidence is similar to what you are describing for all the other supplements out there."

Vol. II pg. 68 Dr. McCausland
"And I support the Working Group's last conclusion [1995], 25 milligrams per dose, 100 per day."

Vol. II pg. 68 Dr. McCausland
"What changes is compromise. The facts don't change."

This is science filtered through political considerations, which is not science at all.

Vol. II pg. 176 Dr. Ziment
"God created the world in seven days, or he rested on the seventh day, and I guess that's where the inspiration for seven days came from, but there's no other pharmacologic reason that I know of."

Amen.

Vol. II pg. 189 Dr. Wang
"I thought since in the OTC drugs ephedrine is allowed to consume, what, 150 milligrams per day on the sustained release product, maybe a 10-fold safety factor, following the Canadian way, is 15 milligrams per day for food, but again I am just pulling that as a figure." (emphasis added)

Ah, an admission that this is the very model of decision making that is arbitrary and capricious, and not in accord with the evidence. Moreover, in so far as the "Canadian way" is involved, this is also a violation of both the APA and FACA (Federal Advisory Committee Act). Moreover, many substances that are ingested would fail this arbitrary and capricious 10X safety criteria, including oxygen and water. Furthermore, DSHEA does not authorize FDA to require a 10X saety factor.

Vol. II pg. 154 Dr. Croom
"I would recommend, if I was doing the recommending, for total ephedrine alkaloids 10 milligrams per dose, which is at the low end of even combinations, 40 daily, and for ephedrine 8 milligrams a dose, 32 daily. Some of that is hearing the Canadian experience and some of that is going with when I'm looking for more at safety here..."

This is the sort of politcs that disgusts both Dr. McCausland and most other close observers of the FDA.

Vol. II pg. 155 Dr. Croom
"To enhance safety, I think from the data to date I would say no xanthine alkaloids in any form, no stimulant laxatives, and no ingredients, of course, that are MAO inhibitors." (emphasis added)

We, like Dr. Croom on Vol. II pg. 105, would allow methylxanthenes such as caffeine in products with a lower ephedra alkaloid per dose limit, 10 mg ephedrine in 15 mg. total ephedra alkaloids, whereas without methylxanthenes, Dr. Croom's pg. 105 original dose limit suggestion of 20 mg. ephedrine in 25 mg. total ephedra alkaloids per dose is thoroughly appropriate. We

also agree that there should be no stimulant laxatives and, of course, no MAO inhibitors.

Vol. II pg. 190 Dr. Blackburn
"I want to see whether if we vote for any of these levels, recommended levels that have come down 10-fold in 2 days, or in 10 months [since the 1995 working group meeting], down to 2 milligrams, what we're really doing, and I think only the people from the industry can tell us. Then if we know what we're doing, then we go ahead and do it. If we reduced it to those kind of doses with these kind of restrictions and this sort of quality control, is there going to be any market and are we banning the drug for use as a good supplement, in which case we might as well go and vote that way?"

But, the banning of ephedra herb products is not possible under DSHEA because the FDA has only very poor quality and unconvincing evidence that using ephedra herb products per label instructions poses a substantial and unreasonable risk to those using it. It cannot meet its burden to prove these alleged risks. Hence, the FDA now wants to reduce the permitted label single dose and permitted label total daily dose and permitted label number of days of use so that none of the benefits of using ephedra will be obtainable by consumers, thereby causing these troublesome (to the FDA) products to dissappear from the market. This is a ban by the back door.

Vol. II pg. 209 Dr. Jasinski
"...my view is that you're probably going to wind up with a dose of no more than 40 to 60 milligrams of total ephedrine alkaloids per day. The reason for this, just doing this and coming back again, from being a pharmacologist and a clinical psychopharmacologist and looking at this in terms of what we know about ephedrine, we know that from studies which have been done over the last couple of years that you can take anhydrous caffeine and give it to people and get amphetamine-, cocaine-like effects, maximizing at about 200 milligrams, between 100 and 200 milligrams."

Right. Note that the FDA approved dose of caffeine in OTCs like NoDoz is 100 mg. to 200 mg. An unwanted overstimulating effect would be particularly noticeable to an adult who had not experienced coffee before, just as most adults in the U.S. probably have not experienced ephedra herb before. However, in the U.S., most adults already have tried coffee and, if they had an unpleasant reaction, avoid it.

Vol. II pg. 210 Dr. Jasinski
"...somewhere about 2.5 milligrams of amphetamine...is equivalent to about 10 to 15 milligrams, 12.5 milligrams, of ephedrine. So one would look at this to keep it in this dose range of what people are using as the average or maximum sort of caffeine dose."

Vol. II pg. 221 Dr. Ricaurte
"I think it's telling that just from October '95 until here we are 8, 9, 10 months later, we've already gone from an estimated safety level down 10-fold, and I'm not quite sure on what basis we're doing this."

Vol. II pg. 222 Dr. Ricaurte
"With the issue of a margin of safety, I'm left at somewhat of a loss because for a margin of safety you really have to have some indication and what I've heard this afternoon is that all purported purposes of use are being taken off the table and it leaves you with, well, what the heck are we going to use this for. If there's no clear answer to that, then the margin of safety, quite frankly, has to go to infinity because you can't do a risk/benefit when we don't have a perceived benefit." (emphasis added)

The FDA has made this conclusion inevitable by **requiring that the committee disregard** any evidence concerning the efficacy of ephedra for those purposes for which it is being most widely sold: weight loss and energy. When you cannot consider any benefit, then of course even small risks will seem unacceptable.

Vol. II pg. 222 Dr. Ricaurte
"Question number 3 [the possibility 'of significant harm' and 'serious adverse effect in at least one individual']--I'm not sure that there's many compounds that can satisfy that requirement, so the answer is, no, I can't, but I'm not sure that it's entirely a fair question with regard to the ephedra alkaloid per se."

And it is not the definition of harm mandated in DSHEA, either.

Vol. I pg. 145 Mr. Israelson
"... the standard you are asking us to look at is significant harm, which has two sub-definitions, I'm just curious how you arrived at that definition, specifically in its two subparts, which is different from the statutory definition within the law." (emphasis added)

Because FDA has chosen to charge the Committee with a definition of harm contrary to that intended by Congress, FDA must withdraw the Rule, re-convene the Committee, reach a new conclusion that fits within the ambit of Congress's will, and re-propose a new Rule.

Vol. II pg. 231 Dr. Ziment
"So my recommendation is that ephedrine, as such, has always been prescribed by orthodox physicians in a dose of about--a minimal dose of 15 milligrams 3 times a day for adults and proportionately less for children. That should be the baseline dose for the orthodox, and I believe it's safe even if used for a prolonged period of time because I certainly used it that way. I've looked at the literature and I don't see much evidence that that dosage is harmful."

Vol. II pg. 236 Dr. Wang
"What margin of safety? What I did is just took a 10-fold safety factor from the OTC maximum level per day basis for, again, ephedrine alkaloid."

It would be interesting to consider what would be left on the market if all products had to be taken on the basis of a 10-fold safety factor. Oxygen, water, sugar, and total daily caloric intake all fail the tenfold safety test. DSHEA does not authorize the FDA to impose a 10X safety margin, either.

Vol. II pg. 249 Dr. Jasinski
"Thirdly, I think there is a telling point which was made that you have to be very cautious. I have been both historically and been involved in people that have made decisions that have driven things underground. I think what amazed me is watching the anabolic steroids of people passing laws because they got concerned about athletes using these. We have now a whole underground economy with anabolic steroids being imported which are being used which are less pure than those which were manufactured as pharmaceuticals coming in, and that's creating public health problems and uncertainties."

Remember that Dr. Jasinski is an expert on drug abuse. Heed his warning.

Vol. II pg. 249 Dr. Jasinski
"And I would think it would be better to encourage industry to come in with a position which they can defend on what they're going to do voluntarily and that this would be legitimate to set the standards. It would be much better than trying to impose a policy."

Far better, and far more effective. The FDA seems to think that if it makes a rule and points enough guns at enough people, any rule will work. This one won't. It will cause far more harm than it prevents, an all too common result at the FDA.

Vol. II pg. 250 Dr. Croom
"We've got to find a better way, I would say, to come together and talk about how do we impact the public health because there are benefits coming here and not just risk..."

Vol. II pg. 255 Dr. Dentali

"When I came here, I understood that my mission is the common-sense one, is to reduce the risk with these products. So when I got the updated version of the adverse events, I wanted to do a rigorous analysis of those, particularly with respect to the October [1995] recommendations. For me, that would be to look at the adverse reactions that are consistent with ephedrine use and to eliminate the ones that are not, to look at ones that are consistent with the levels of ephedrine that were recommended in October or that were proposed by a few members and eliminate those that were not, to look at the ones that were combined with other known stimulants and eliminate those reports, to look at the ones that were resulting from clear abuse and to eliminate those, to look at the ones that were made with only the herb and the herb extract and to include those and exclude all the others, and to exclude the ones that were resulting from chronic use. And I feel that that wasn't done and I feel that that was very important for me to be able to have a handle on beginning to look at the risk as it was presented to me regarding the adverse effects for us to determine for traditional use and traditional forms what is the danger of using this botanical."

A very cogent objection.

Vol. II pg. 262 Dr. Ricaurte
"So the pendulum has swung from one extreme of being very cynical to trying to regard this as a product, a dietary ingredient that should be used by consumers and not be over-regulated, not be in a position where the FDA or the medical profession or the scientific advisory group is put into a position of over-regulating something that adult Americans may wish to use under safe conditions. Those have not been defined."

Vol. II pg. 262 Dr. Ricaurte
"I think as long as the concern for some of the use is misuse and abuse, I find it somewhat, again, disingenuous to make recommendations, well, we're going to limit the dose from 20 down to 10 or down to 5. As a consumer, I don't have to be particularly adept in mathematics to realize that if now the

tablet or capsule or a spoonful contains only 5 milligrams, I take 2 or I take 3 or I take 4. So the dose considerations and frequency of use suggestions, while I recognize that they're well-intended and I appreciate what the efforts are in terms of looking at the reality of the use of the product by a population of individuals who may be predisposed to misusing or abusing the product, I don't think those are particularly effective safeguards."

They are worse than ineffective; they will substantially increase the risk of harm by destroying the integrity and credibility of all the label instructions and warnings on ephedra dietary supplements.

Vol. II pg. 265 Mr. Israelson
"...I share the view that has been expressed that if you ban this product, you'll drive it underground and create a bigger problem."

Vol. II pg. 270 Dr. Woosley
"...as I think you pointed out, Dr. Ricaurte, there is no risk/benefit ratio you can establish when you don't have a known benefit..."

There are benefits known to the Committee; the FDA just refuses to allow the Committee to consider them, thereby guaranteeing a proposed Rule that is not based on reason or evidence.

Vol. II pg. 274 Dr. Inchiosa
"...in the experiences in Ohio, the Canadian study, even the information collected was that young people who are abusing the drug largely get it from ephedrine hydrochloride from over-the-counter preparations. I heard that statement made that a large number of the use by young and abuse by young was from over-the-counter preparations, not the difficult process of extracting something from a nutritive supplement."

Vol. II pg. 197 Dr. Kessler

"It's [the judgment on a safe level of ephedrine] based on the record before individuals. We have alot of different individuals with a lot of different expertise. We'll take that into account. For some, it'll be the information that has been presented over the last two days. For some, it'll be information that has been presented both in the working group and over the last two days. For others, they certainly can draw upon the literature that they're familiar with and their own expertise, but it's the record before them as has been presented. I think that the starting base is over the last two days, certainly."

But the data supplied over the last two days is of very poor quality and, as admitted by Dr. Love, has not yet been peer reviewed. Moreover, vital OTC adverse event safety data has been expressly removed by the FDA.

Vol. II pg. 204 Dr. Chassy
"We are talking about a dietary supplement which I as a consumer, when I walk into a store that sells these products, have every reason to believe are at least as safe as the foods in my diet that I mean to supplement and so I would hold them up to a very high standard of expected safety."

As we have shown, ephedra herb dietary supplements are already much safer than foods in common form. The bottom line is that consumers have unrealistic beliefs about the presumed safety of foods and need badly to be educated about that. Educating consumers about the risks of foods is of far greater importance than that of dietary supplements, on the basis of the record, yet the FDA has done a very poor job of providing needed information on food risks to consumers.

Vol. II pg. 157 Dr. Jasinski
"...the critical question has been the relationships of these deaths and your data and the particular interpretation versus the interpretations we've heard, and there has been a conflict."
"...and the essence of the scientific culture is we have peer review." (emphasis added)

Vol. II pg. 158 Dr. Jasinski
"My question is have you prepared a report on your data, how you collected it, how you interpreted it and what conclusions you've made, and have you submitted this to internal review within the agency or outside the agency? And, similarly, have you taken the report from this ad hoc committee and submitted it to a peer review?" (emphasis added)

Vol. II pg. 158 Dr. Love
"We, of course, intend to do that, but we were analyzing this data even over the weekend to supply the information to you at this committee meeting here." (emphasis added)

They were in such a tight schedule that they didn't have time to do the internal review or submit the data and their conclusions to peer review. So they just rushed into the meeting without that. Where is that peer review that they intended to do?

Vol. II pg. 248 Dr. Jasinski
"...I have been disturbed to some extent by what is really the lack of either scientific scholarship or scientific quality through all of this. ...it's like the question I asked Dr. Love in terms of did she write a report, was it reviewed, was it peer reviewed, making this available before you start getting these discussions." (emphasis added)

Vol. II pg. 26 Mr. Betz
"...although I pointed out last time [meeting in 1995] that these three products contain absolutely no ephedrine alkaloids, they're still in the report as part of this larger report."

The report that the FDA provided to the Committee was carefully purged of data pertaining to OTC drugs containing the same ephedra alkaloids as the dietary supplements, but apparently little or no care was taken to remove adverse reaction reports for dietary supplements that contained no ephedra alkaloids whatsoever. The FDA's report would never pass peer review. It must be noted that the FDA report as given to the Committee would

not meet the Supreme Court's Daubert criteria for weeding out junk science.

Vol. II pg. 53 Mr. Shapiro
"...it has also been widely reported that the individual [college student who died in Florida] ignored clear warnings on the product and took at least twice the daily dose all at once. Those same reports indicate that his companions all took three times the daily dose without incident. In addition, according to the police report, cannabis and another product, Nexus, consisting of the herb kava-kava were found in the hotel room." "It is noteworthy that the autopsy report contains no findings at all relating to the presence of other substances such as cannabis, cocaine, amphetamines or barbiturates. It appears that no tests were performed for the presence of these and other substances which is most certainly very strange." "Yesterday, Dr. Love said that the tests were performed. If so, the results were not made a part of the autopsy report." (emphasis added)
"The Ad Hoc Committee on the Safety of Ma Huang submitted to you as part of their package the declaration of Dr. Joseph Brazelica, a toxicologist, which sets forthe many deficiencies in the autopsy report and concludes: 'That it is not possible to determine from the report of autopsy to a reasonable degree scientific certainty that the cause of death was the ingestion of some quantity of a product containing ephedrine.'" (emphasis added)

Vol. II pg. 110 Dr. Askew
"Clarification of the autopsy." (This refers to the autopsy mentioned earlier in which there was some question as to what the coroner found in the consumer's bloodstream.)

Vol. II pg. 110 Dr. Love
"The clarification of the autopsy report is that information on the consumer's negative ethanol and cannabis levels are in the record."

Vol. II pg. 147 Dr. Love
Dr. Love clarifies the Florida autopsy report, which found ephedrine alkaloids and caffeine positive, while a long list of others tested for were negative, including cocaine, amphetamines, strychnine, cardioregulatory drugs, and others.

Vol. I pg. 229 Dr. Fukagawa
"...in letters that we've received from Mr. Appler from the Ad Hoc Committee on the Safety of Ma Huang and from Mr. Shapiro at Bass and Ulman, who also referred to the 20 year old from Florida, suggest that his situation was perhaps not as clear-cut with the presence of other compounds in his hotel rooms etc., and the lack of toxicological reports or analyses." (emphasis added)

Vol. I pg. 229 Dr. Love
"Actually all of his blood levels for anything else were negative, and the coroner directly attributed it to the use of this product." "Now, where is the exception is this is the highest level of ephedrine alkaloids that we have analyzed in any product." (emphasis added)

Why didn't the FDA show the autopsy report? Mr. Prochnow said that this data was not in the autopsy report.

Vol. II pg. 65 Dr. Calvin McCausland from Enrich International, Orem, Utah
"...if you look at the 20-year old in Florida and the autopsy report, you will find reasonable doubt. That reasonable doubt has been spelled out by Dr. Borzelica, from the Medical College of Virginia and it's in those three volumes that you have before you." "There are other deaths that have been listed that have reasonable doubt. They took ephedrine a week before, reportedly. There is none in the tissues of the autopsy. Reasonable doubt."(emphasis added)

Vol. I pg. 59 Michael Davidson, M.D.
Dr. Davidson's qualifications and his review of the adverse event reports on behalf of the NNFA. See Adverse Event Clinical

Summaries at Tab F referred to by Dr. Davidson. He reviewed the case files underlying 191 of these adverse event summaries. Of these 191 case files, he categorized 84 of the events to be serious and 107 not to be serious. "Of the 84 serious events, I found that 13 were not related to ephedra. I classified eight as unknown for lack of information. Thirty-four were remotely related; 22 were possibly related, and seven were probably related."

pg. 61 "Six deaths were possibly associated with ephedra. In two cases, not enough information was provided to consider an assessment. Two deaths were related to consumption of toxic doses of ephedra." "Of the six deaths possibly associated with ephedra, three were due to sudden death and cardiac abnormalities were present on autopsy in all three individuals. Two of the possibly associated deaths were due to strokes. One of these deaths was due to a strong [stroke?] that occurred in an obese individual male who was using multiple other supplements and who had basilar artery atherosclerosis on autopsy. Another was a fatal stroke that occurred in a 44 year old female due to a left internal carotid artery occlusion. She had a very strong family history of strokes. The sixth possibly associated individual whose death was from a seizure was also on phenteramine, Apidex, a prescription drug for weight loss. All of these six possibly associated deaths occurred on the high dose ephedra products." [How high?]

"There were ten cases of non-fatal myocardial infarction. Of these ten cases, four, in my judgement, were not related to ephedra. In another three reports, there was not enough information provided to make an assessment. In three cases of myocardial infarction, a possible association with ephedra exists. In all three of these reports, post-myocardial infarction angiograms revealed normal coronary arteries. All three individuals were consuming high-dose ephedra in combination with caffeine.

There were 17 reports of non-fatal strokes. Three cases were unrelated or remotely related to ephedra-containing products. In four additional cases, not enough information was available for

me to make an evaluation. In the remaining ten cases, a possible association with ephedra products exists.

In four of the ten possibly associated cases, these individuals had significant hypertension of hyperlipidemia diagnosed prior to the stroke. One case involved a male with a dilated left ventricle as a possible source of emboli. The remaining five cases involve premenopausal women. At least two of these women were on oral contraceptives. One of these was noted to be a cigarette smoker and the other was diagnosed as having a positive lupus inhibitor. In the three remaining possibly associated cases, oral contraceptive use is unknown and one was a cigarette smoker, and one of these women was on the product for over a year before she suffered as intracerebral hemorrhage. All but one of these stroke patients--the exception being the woman with a positive lupus inhibitor--were on the high-dose ephedra containing products.

There were 16 reports of seizures. Of these cases, the majority of seizures occurred in individuals with either a history of seizures or an abnormal EEG on follow-up. As I am not a neurologist, I made only a limited evaluation of these cases.

In summary, with the exception of two cases of toxic exposure to ephedrine, there appears to be only infrequent possible associations of ephedra-containing products with severe adverse reactions. These infrequent possible associations are characterized by coronary or cerebral thrombosis and seizures.

Of the 105 non-serious adverse events that I reviewed, these are characterized by increases in blood pressure, tachycardia, nervousness, and dizziness. These symptoms are expected potential side effects of ephedra-containing products. These side effects appear to be dose-related, occurring in greater frequency in the high-dose ephedra-containing products.

To test the hypothesis that low-dose ephedra products below 15 mg. per dose, which is the recommended dose of the working panel, do not have a significant rate of adverse events, I reviewed the adverse events associated with the ephedra product containing less than 15 mg. per dose. These products account for over one-third of all the ephedra-containing products, but only

approximately 7% of the adverse events. Of these 42 adverse events on low-dose products, there were only two serious events that were possibly related to the product. I mentioned one was the young woman who had a stroke who also had a positive lupus inhibitor, and the other was a 55 year old female who had a seizure.

Based on my medical review of the ephedra adverse event reports, I have the following opinions:

Number one, last year's [1995] recommendation of the ephedra working group and those of the dietary supplement trade associations are appropriate. The two main issues that appear to affect adverse reactions are the dose of the ephedra and the quality assurance of the product.

The proposal to lower the ephedra alkaloid content to 60 mg. per day with 15 mg. of ephedra per dose, expressed as ephedrine equivalents, provides a margin of safety based on the fact that the vast majority of both serious and non-serious adverse reactions occurred with products that exceeded these dosage thresholds.

Improved good manufacturing practices and quality assurance will provide dosing consistency within product batches. Because dosing consistency is important, I would add to the recommendation that products that can be easily mis-dosed not be permitted. (emphasis added)

The ephedra working group also recommended very appropriate warnings and labeling instructions. I would also include on the label cautions against the use by smokers, those taking oral contraceptives, and those with a history of cardiovascular or seizure disorders.

Vol. II pg. 107 Dr. Georgitis
"Dr. Love, I have a question for you, in terms of the serious aadverse events below the median value of 20 milligrams per serving of the ephedrine alkaloids, do you have a percentage as to how many of those out of the total adverse events?

Vol. II pg. 107 Dr. Love

"We haven't expressed our data in that form because, of course, we have only a relatively few samples where we've been able to collect the sample that the consumer was using at the time of the injury and be able to analyze that." (emphasis added)

This is clearly a very important question concerning how the numbers of reports of adverse events related to the amount of ephedrine actually consumed. Here, the FDA admits that it doesn't know that. This is a very poor reflection on the follow-up of the FDA after receiving such reports.

Vol. II pg. 108 Dr. Kessler (to Dr. Love)
"...you asked for relatively clean cases that didn't have a lot of confounding factors--where you have a medical examiner, where you have a sample--could you just go through those cases and at what levels you saw significant adverse reactions?

Vol. II pg. 108 Dr. Love
"Well, unfortunately, I don't have all the data in hand here, but there are a number including very recent cases for which we yet don't have all information on how the consumer used the product but a more recent death, again, it appears to be a cardiomyopathy case. The total alkaloids in that case are 10 milligrams, total alkaloid. As I stated a death from what appears to be long-term use of a product containing 10 milligrams of total ephedrine alkaloids."

The FDA here mentions a single case of what "appears" to be long-term use of a product containing 10 milligrams of total ephedrine alkaloids. No information is provided on what else the individual was taking or how the FDA knows how much of the product the individual was using, or how often.

Vol. II pg. 109 Dr. Kessler (to Dr. Love)
"And just go through that case. I mean just so we have some--I mean the best data that we have."

Vol. II pg. 109 Dr. Love
"Well, as I stated I don't have all those details."

Vol. II pg. 109 Dr. Kessler (to Dr. Love)
"I'm sorry."

This is a shockingly small amount of total information on what is supposed to be their best or one of the best cases providing evidence concerning adverse reactions versus dose.

Vol. I pg. 228 Dr. Chassy
"I'm trying to get at something that gives us some feel for where we begin to see a dose-response correlation, because as it stands now, you have effects all across the board. But you do have fewer products with very high amounts of ephedrine alkaloids in them, and where you have fewer of those products on the market, you seem to have around the same number of cases of adverse effects reported, which suggests that there is a dose-response relationship."

Vol. I pg. 234 Dr. Jasinski
"...you're showing this increase [in relative incidence], and how much of this increase is actually an increasing showing that we're getting a growing public health problem that's going to project, or how much of this increase is related to the change in the way you've done things in publicizing this and asking people to report in?"

Indeed, the FDA's publicity concerning the adverse events reports they received in which injuries were associated with (but not necessarily caused by) the use of ephedra alkaloid containing dietary supplements has resulted in reports on CNN and a recommendation not to use ma huang in the July 1997 Reader's Digest (pg. 85). The FDA's warnings have also appeared repeatedly on network TV. There has been no similar FDA publicity during this period concerning adverse events reports the FDA has received for ephedra alkaloid (ephedrine, pseudoephedrine, or phenylpropanolamine) containing OTC products.

Vol. II pg. 277 Mr. Guzewich

"...I want compliment Dr. Love on what she's trying to do in running a surveillance program. I've been doing that for 16 years for food-borne disease. It's not an easy task and she has a very difficult and often thankless job, and you're reporting for poor quality data and when it's the only data you can get ahold of and you're trying to make decisions on that kind of data..."

Yes, the data are poor quality, and the FDA cannot improve the quality of these data by dumping them into the lap of a hapless committee, which is then told to ignore any benefits of the products. Moreover, the FDA failed to present the committee with other available and important information. The FDA could have prepared a report on the adverse events and had the data peer-reviewed, but it did not. The FDA should have had data available on the spontaneous occurrence of MIs and strokes and seizures in the population using the ephedra products, but did not. The FDA should have had data available on the occurence of adverse side effects in the OTC ephedrine containing drugs for comparison, but they did not.

Vol. II pg. 282 Mr. Guzewich

"...sophisticated choices about products that might be at risk to them, I think, is more than we can reasonably expect consumers to have to assess when they choose between different bottles on the shelf. Therefore, consumers should be able to purchase a product in the market and find it safe at normal use, and <u>even</u> <u>at</u> <u>abused levels</u>..." (emphasis added)

More and better information on labels and in labeling and other methods of education for consumers so that they can make choices is a far better and safer choice, in our opinions, than to treat consumers as unmitigated idiots that must have decisions made for them by committees assembled by the FDA and given by the FDA poor quality data and unreasonable limitations (eg., do not consider any benefits) to make decisions for them. The final point made by Mr. Guzewich, that a product in the market should be safe at virtually any dose is impractical and ridiculous. Consumers must be expected to assume some personal responsibility for their use of products, at least extending to their compliance

with label instructions. Moreover, DSHEA requires that dietary supplement products not be unreasonably unsafe when used as directed, not to be safe no matter how badly abused.

Vol. II pg. 285 Dr. Chassy
"Several [committee members] have noted the quality of the data, and without blaming the FDA staff in any way because they are to be commended, they need to build a cause-and-effect relationship, however hard that may be. I think they especially need to do it because DSHEA sets us in a situation where they [FDA] may find themselves in court being asked to bear the burden of proof that the ephedra alkaloids have done damage in a specific case, and they may find themselves doing that again and again and again."

The above comment speaks for itself. FDA data from this Committee meeting would never meet the Supreme Court's Daubert criteria for weeding out junk science. Because of this, FDA must withdraw the Rule, re-convene the Committee, provide sound peer reviewed data to the Committee members in advance, reach a new conclusion that fits within the ambit of Congress's will, and re-propose a new Rule.

It doesn't seem that the thousands of pages of materials that the FDA presumably distributed to each of the committee members before the meeting were actually read by most of them, judging by the questions asked of the FDA during the meeting. These questions included what are the background numbers of cardiac deaths and seizures among the population using ephedrine-containing dietary supplements and what were the levels of adverse reports for OTC products containing similar amounts of ephedrine as ephedrine-containing dietary supplements).

The answers to these questions are key information in interpreting the meaning of the adverse reports. Yet, at the meeting, Dr. Love (FDA) did not have this information. Either the committee members did not do their homework or the FDA did not have key information available either before or at the meeting or both.

SPECIFIC PROPOSAL FOR A CONSTITUTIONALLY ACCEPTABLE LABEL

The FDA cannot ignore the limits placed on it by the First Amendment of the U.S. Constitution. We have discussed these limitations at some length (often quoting Supreme Court Justices) in a prior section on general labeling considerations. The FDA has no constitutional authority to prohibit statements that are true and not misleading. The FDA does have the authority to prohibit statements that are false or misleading, and to require reasonable disclosure of hazards on the labels and labeling of dietary supplements sold in interstate commerce. This discussion considers the application of these limits and powers to a specific product.

Commenters Pearson & Shaw license formulations containing approximately 1.8 grams of ground ephedra herb per one tablespoon serving (the amount of ephedra herb being adjusted on the basis of herb lot analyses so that one tablespoon of product contains a total of 20 mg. of ephedra alkaloids). No ephedra extracts are used in this product, there is no caffeine or other methylxanthines, and it contains no synthetic ephedrine, pseudoephedrine, or phenylpropanolamine.

Since whole ground herb is used rather than an instantly soluble ephedra alkaloid extract, blood levels of the alkaloids increase much more slowly as the ground herb slowly releases its alkaloids, thereby providing a time-release effect and reducing the risk of adverse effects in sensitive individuals.

Products containing real ephedra herb when ingested are pharmacokinetically substantially different from products containing ephedra alkaloid extracts; regulating them in an identical manner is arbitrary, capricious, and contrary to fact.

With a one tablespoon serving, this product contains approximately 1.8 grams of ephedra herb (adjusted to standardize

the amount of ephedra alkaloids) per serving of tea, quite conservative compared to the traditional tea serving of 1.5 to 9 grams (usually 5 to 6 gm.) of ephedra herb referred to on page 20 of the proposed Rule.

On the basis of the FDA's proposed Rule, we propose the following new label for this product:

NOTICE: CONTAINS EPHEDRA HERB WHICH CONTAINS EPHEDRINE ALKALOIDS.
FDA MANDATED SERVING SIZE:: 1 TEASPOON (contains 6.7 mg. total ephedra alkaloids). The FDA believes that a serving size of 8 mg. or more would present an unreasonable risk of injury or illness. Taking more than this recommended serving may cause heart attack, stroke, seizure, or death.
TRADITIONAL SERVING SIZE: 1 TABLESPOON (contains 20 mg. total ephedra alkaloids from approximately 1.8 grams of herb). This serving size is **NOT** approved by the FDA.
DIRECTIONS: Add 4 ounces of hot or cold water to one serving of mix. Stir briskly and drink. **DO NOT EXCEED THREE SERVINGS A DAY!** On the first day, drink one-half serving before breakfast. For the next two days, drink one serving before breakfast. For the next three days, drink a second serving before lunch. From then on, drink a third serving one hour before dinner. Do not take more than one serving within a 6 hour period. Keep in a cool, dry place. Keep lid tightly closed when not in use.
FDA MANDATED INSTRUCTIONS: Consult a health care provider before use. Do not use this product for more than 7 days. Risk of adverse reactions increases with duration of use. Starting and stopping use may increase risk of adverse reactions.

WARNING: KEEP OUT OF REACH OF CHILDREN. NOT FOR SALE TO OR USE BY PERSONS UNDER THE AGE OF 18. DO NOT EXCEED RECOMMENDED SERVING SIZE OR FREQUENCY. May cause insomnia in sensitive individuals, especially if taken too soon before bedtime. Consult your physician before use if you are taking asthma medications, decongestants, anorectic (appetite suppressing) drugs, antidepressants, or cardiovascular medications. Use of caffeine

containing beverages may increase the stimulating effects of this product. Do not use this tea if you are pregnant or lactating, if you have high blood pressure or cardiovascular disease (especially stroke or cardiac arrhythmia) or a family history of these disorders, diabetes, difficulty in urination due to prostrate enlargement, seizure disorder, glaucoma, hyperthyroidism, or psychiatric disease. Do not drink this tea within 14 days after taking MAO (monoamine oxidase) inhibitor drugs. Stop use and call your health care professional if dizziness, headache, heart palpitations, or tingling sensations occur. Stop use or reduce serving size if sleeplessness, tremors, nausea, or nervousness occurs. Stop use if symptoms of allergy to this product develop.

Note that these instructions increase the serving size from the initial one-half of 6.7/20. mg. ephedra alkaloids once per day to the final 6.7/20 mg. three times per day **over a period of seven days.** This schedule is designed to reduce the incidence of adverse effects by allowing the development of tolerance to the CNS and cardiovascular effects of the ephedra alkaloids.

The Caution on page 43 of the proposed Rule has been modified in several respects:

1) "Warning" is used rather than "Caution," as is tentatively proposed by the FDA.

2) Rather than "Seek advice from a health care practitioner if you are pregnant or nursing or if you are at risk or are being treated for high blood pressure, heart, heart, thyroid or psychiatric disease, diabetes, seizure disorder, stroke, or difficulty in urination due to prostrate enlargement." these and other conditions are all listed as "Do not use if..." absolutely contraindicated conditions. We do not believe that these conditions should be required as absolute contraindications (rather than checking first with your doctor), as we have expressed it, but the stronger form of warning we have used

should not be prohibited. **It would be arbitrary, capricious, and not in the public interest for the FDA to standardize the warning in such a way as to prevent the listing of additional contraindications or to prevent contraindications from being listed as absolute rather than relative. FDA should require a minimum list of contraindications but must never prohibit additional or stronger contraindications than their minimum required list.** For example, rather than "Consult your health care professional before use if you are taking an MAO inhibitor or any other prescription drug." we believe that we should be permitted a label warning that taking an MAO inhibitor within the last 14 days is an absolute contraindication.

3) "Taking more than the recommended amount will not necessarily increase benefits." has not been used because it is both weak and lacks credibility. Worse yet, this lack of credibility may tend to reduce the credibility of the other warning statements. Instead, we have used the FDA's much stronger warning: "The FDA believes that a serving size of 8 mg. or more would present an unreasonable risk of injury or illness. Taking more than this recommended serving may cause heart attack, stroke, seizure, or death." We do not believe that this stronger warning should be required, but the FDA should not prohibit a stronger warning than the one that is proposed.

4) We have not instructed the user to consult with their health care professional if they are taking <u>any</u> prescription drug. Such consultations may easily cost $50 or more; people will generally ignore this warning. It is unreasonable to expect customers to take this action; they simply won't do it. It is unwise to put a warning on the label that one knows will be generally disregarded, for such warnings promote a general disregard for other far more important warnings. As an alternative to this ineffective warning, we believe that we should be allowed to say "Consult your physician before use if you are taking asthma medications, decongestants, anorectic (appetite suppressing) drugs, antidepressants, or cardiovascular

medications." If the FDA Rule requires the label to carry "Consult your health care practitioner before use if you are taking an MAO inhibitor or any other prescription drug," this statement will be prefixed with the truthful non-misleading "FDA mandated Warning:", which is protected speech under the First Amendment.

5) Users of ephedra dietary supplements should not be instructed to call a physician if "sleeplessness, tremors, nausea, or nervousness occur," since these are not likely to be precursor symptoms of a potentially serious or life-threatening adverse reaction. Instead, they should be instructed to "stop use or reduce serving size." If users are instructed to make an expensive call to their doctor because of a minor matter like temporary insomnia, they are less likely to call their doctor when "dizziness, headache, heart palpitations, or tingling sensations occur," which may be symptoms of far more serious problems such as hypertension, stroke, or a potentially serious cardiac arrhythmia. There is a very real cost to diluting major warnings with minor warnings. If the FDA's Rule requires the label to carry their preferred warning, it will be prefixed with the truthful non-misleading "FDA mandated Warning:", which is protected speech under the First Amendment.

6) **The split label:** This label identifies FDA mandated information as such. This label contains two different serving sizes, one mandated by the FDA and identified as such, and an alternate serving size that provides a traditional amount of ephedra herb per serving.

Identifying FDA mandated information as such is truthful and non-misleading. Indeed, without such identification, the customer would be misled into believing that the product manufacturer voluntarily agreed with this information and had voluntarily placed it on the label. FDA has no constitutional authority to prohibit the truthful identification of the FDA as the source of this information and its mandatory nature.

The FDA mandated serving size is one teaspoon containing 6.7 mg. ephedra alkaloids. This serving size is clearly identified as being recommended by the FDA. Moreover, the FDA's reasons are clearly and forthrightly stated, "The FDA believes that a serving size of 8 mg. or larger would present an unreasonable risk of injury or illness. Taking more than this recommended serving may cause heart attack, stroke, seizure, or death." This is the strongest warning regarding serving size that the FDA has proposed in the Rule. If this were the only serving size described on the label, we believe the FDA would have no objections.

The traditional serving size is one tablespoon containing 20 mg. of ephedra alkaloids. It is in fact at the low end of the traditional ephedra herb dosage range. The statement that this is a traditional serving size is truthful and non-misleading; the FDA has no constitutional authority to prohibit it. An FDA prohibition of this traditional serving size statement would be a content based prior restraint caused by FDA's not wanting people to know this information. The FDA doesn't want people to know this information, because if they learn of it, people may not behave the way the FDA wants; customers may choose to take the larger servings rather than the FDA's preferred smaller ones. The First Amendment prohibits the manipulation of consumer behavior by restricting the communication of truthful, non-misleading information.

Quotes from the U.S. Supreme Court decision in 44 Liquormart v. Rhode Island (1996 WL 241709 (U.S.))

"...a State's paternalistic assumption that the public will use truthful, non-misleading commercial information unwisely cannot justify a decision to suppress it." (at 8)

"It is precisely this kind of choice, between the dangers of suppressing information, and the dangers of its misuse if it is freely available, that the First Amendment makes for us." (quoting from Pittsburgh Press Co. v. Pittsburgh Comm'n on Human

Relations, 413 U.S. 376, 93 S.Ct. 2553, 37 L.Ed.2d. 770 (1973)

"In case after case following Virginia Pharmacy Bd., the Court, and individual Members of the Court, have continued to stress the importance of ... the impropriety of manipulating consumer choices or public opinion through the suppression of accurate 'commercial' information..." (J. Thomas, concurring, at 21)

The First Amendment of the US Constitution absolutely prohibits the FDA from banning labeling that is neither misleading nor deceptive. Indeed, Pearson & Shaw, et. al, have a First Amendment lawsuit against the FDA Commissioner before the U.S. District Court for the District of D.C. at this very moment. (Civil Action No. 95-1865 (EGS), District Court for the District of Columbia) If the FDA proceeds with its proposed Rule, it is likely to be sued again.

Note, too, that this product does not describe any non-traditional uses (or indeed, any uses at all) on the label or labeling. Nearly all customers of this product use it before meals to help satisfy appetite (the reason most foods are eaten) as an adjunct to their own personal weight loss or weight maintenance program.

In addition to considering the constitutional issues that an FDA attempt to ban this label would raise, we suggest that the FDA consider the pragmatic public health value of allowing the vendor to provide a maximum serving size that is likely to be heeded. The FDA's serving size is so small that consumers will generally ignore the FDA's dose limitation. This is especially likely for the many millions of people who have had prior experience with ephedra herb products.

Without an alternate serving size that is more likely to be heeded by the consumer, the consumer may take unnecessary risks. The consumer will know that the FDA has radically reduced the dose of the supplement, so they will take more -- perhaps far too

much more than needed to compensate for FDA's dosage reduction.

For the sake of both liberty and government legitimacy under the constitution, FDA must not attempt to prohibit ephedra dietary supplement labels from displaying truthful non-misleading traditional dose statements.

For the sake of consumer safety, the manufacturers of existing products must not be prohibited from informing the consumer of both the size of the old dose and the new dose. If FDA prohibits the publication of this information on the labels and in the labeling of existing products, they will not only be violating the First Amendment ban on content based prior restraint in an unconstitutional attempt to manipulate the public's behavior by denying them information, FDA will be dramatically increasing the risks to the public of accidental overdose. Moreover, the FDA's credibility will drop further as its actions are scrutinized in public fora such as health newsletters and the Internet.

The alternate serving size provides 20 mg. of ephedra alkaloids, a little more than the 17 mg. median dose and substantially less than the 30 mg. mean dose of products that FDA identified in its market survey, and with which millions of consumers may be familiar. By providing the customer with an alternate serving size near the low end of the traditional dose range, there is a reduced risk of large accidental overdoses taken by consumers who reject FDA's recommended dose but who otherwise don't know how much to take. If the FDA continues to arrogantly delude itself by believing that it can control people's behavior by enforcing ignorance through their proposed rule, they will succeed only in violating the constitution, discrediting themselves, and causing greater risk and harm through uninformed and unintentional gross overdoses.

ONE SIZE DOES NOT FIT ALL:

EPHEDRA HERB IS NOT EPHEDRA HERB EXTRACT

EPHEDRA HERB EXTRACT IS NOT SYNTHETIC EPHEDRINE

FDA'S PROPOSED RULE ANALYTICAL METHOD WILL NOT PROVIDE ACCURATE MEASUREMENTS OF THE BIOAVAILABLE EPHEDRA HERB ALKALOIDS IN PRODUCTS MADE WITH ACTUAL EPHEDRA HERB RATHER THAN WITH EXTRACTS

Food Advisory Committee meeting August 27-28, 1996

When actual ephedra herb is ingested rather than an instantly soluble ephedra alkaloid extract, blood levels of the alkaloids increase much more slowly as the ground herb slowly releases its alkaloids, thereby providing a time-release effect and reducing the risk of adverse effects in sensitive individuals.

Products containing actual ephedra herb when ingested are pharmacokinetically substantially different from products containing ephedra alkaloid extracts; regulating them in an identical manner is arbitrary, capricious, and contrary to fact.

Vol. I, pg. 146 Dr. Jasinski
"...we already know if you put medications in a certain sort of matrix that's natural may alter this from -- the pharmacology from the pure medication in terms of absorption and rate of limitation [elimination?]."

Vol. I, pg. 146 Dr. Yetley
"We are not aware of data on the botanicals that would answer the questions you have." "But those are the scientific issues that we're asking this group of experts to discuss and to make some recommendations on."

Vol. I, pg. 147 Dr. Inchiosa
"The herbs themselves might contribute to affecting the alkalinity of the urine, which is going to affect the half-life of the drug, which is going to influence the steady state plasma concentrations."

Vol. I, pg. 157 Dr. Hsieh
"Do you want us to look at the compounds, or do you want us to look at the herb? And the two should not be equated." (emphasis added)

Vol. I, pg. 158 Dr. Yetley
"I understand that the two are not equated, but both could be ingredients in the products that we're seeing. So you need--the botanical is certainly very common, or at least extracts of the botanical, concentrated extracts of the botanical are very common in these products. But it is also possible that some of these products may have synthetic form, so it's really both." (emphasis added)

Didn't the FDA do any analyses of the products in their market review to determine whether there was synthetic ephedrine added, whether there were any ephedra alkaloids other than ephedrine in them (as would be the case with a genuine ephedra herb extract), and what percentage contained the actual herb rather than an ephedra alkaloid extract?

Even though the FDA's Dr. Yetley correctly states, "I understand that the two are not equated,..." FDA's proposed Rule does precisely that; it treats ephedra herb products exactly the same as ephedra herb alkaloid extract products.

Because of this, FDA must withdraw the Rule, re-convene the Committee, reach new conclusions that correct these errors, and re-propose a new Rule.

Vol. I, pg. 180 Dr. Jasinski
"Just a question of Dr. Obermeyer. What is the extraction efficiency? Have you done this? If you take the herb and make a tea, what is the extraction efficacy?" (emphasis added)

Vol. I, pg. 180 Dr. Jasinski
"I'm not talking about your chemical analysis. If somebody makes a tea, what is the extraction efficacy?" (emphasis added)

Vol. I, pg. 180 Dr. Obermeyer
"That depends on brew time. So if you would steep it for one minute versus three minutes versus someone that forgot it in their tea cup for ten minutes, that would be much different." (emphasis added)

Vol. I, pg. 181 Dr. Jasinski
"What's the maximum extraction efficacy you can do if you make a tea and you put it in the pot and you boil it up?" (emphasis added)

Vol. I, pg. 181 Dr. Obermeyer
"We have not worked on that for the maximum. What we would extract it for would be methanol to be the maximum out of an herb..." (emphasis added)

The FDA has no idea how much of the ephedra alkaloids would actually be extracted and ingested from a cup of tea made with actual ephedra herb (rather than ephedra extract or synthetic ephedrine HCl). Furthermore, the FDA has no idea how much of the ephedra alkaloids would be extracted in the human gut from ground ephedra herb consumed as an iced tea which is consumed without brewing.

The numbers the FDA's Dr. Obermeyer is providing are the results of chemical analysis that have very little if anything to do with how a tea containing actual ephedra herb (rather than ephedra alkaloid extract) is used. There is no hot methanol extraction, either in the consumers' tea pots or in the human GI tract.

Vol. I, pg. 181 Dr. Jasinski
"I mean, the question before the group is, you know, in terms of dose and what you're going to get and what the safe dose is going

to be. If you don't know what people get out of the herb when they brew it, there's no way to answer this question." (emphasis added)

FDA's proposed Rule treats products containing actual ephedra herb exactly the same as products containing ephedra herb extract which is arbitrary, capricious, and contrary to fact. Because of this, FDA must withdraw the Rule, do its laboratory homework, re-convene the Committee, reach new conclusions that correct these errors, and re-propose a new Rule.

Vol. I, pg. 181 Dr. Obermeyer
"Right. Most of the products really are encapsulated or tablets of the ma huang extract. This is what we are seeing mostly. And very few products are actually the herb root as a tea." (emphasis added)

FDA's Dr. Obermeyer here admits that Dr. Jasinski is correct in his concerns that ephedra herb products are not the same as ephedra alkaloid extract products. Dr. Obermeyer also admits that **"very few"** of the products that the FDA is considering in this meeting **"are actually the herb ... as a tea."**.

If the FDA wishes to proceed with their proposed Rule without gathering the needed new data on actual ephedra herb products, holding new Committee meetings, and making major modifications in the Rule and analytical method, FDA should exempt all products from this Rule that contain actual ephedra herb rather than ephedra herb alkaloid extracts or synthetic ephedrine. To apply the proposed Rule to products that contain actual ephedra herb (not ephedra herb alkaloid extracts or synthetic ephedrine) would be arbitrary, capricious, and contrary to fact.

Technical note: Although we have an herbal text which refers to the "twigs and roots" being used in ephedra herb teas, we do not believe that use of the roots is a common commercial practice. Ephedra Sinica (and related species) is a perennial; leaves (which look rather like green twigs or pine needles) and the stems that bear them are harvested, not the roots. By leaving the roots and some of the stems and leaves, the plant's

stems and leaves grow back next spring, and can be harvested year after year. This is particularly important since Ephedra Sinica is a slow growing plant. If grown from seeds or cuttings, several years will pass before the plant can be harvested. We have seen a lot of the ephedra herb that is imported into the U.S., but we have seen only the needle-like leaves and the stems that bear them; we have never seen any ephedra roots.

Vol. I, pg. 184 Dr. Fong
".... The data as I sit here running through my mind is **when you talking about extraction with methanol, and then people taking the capsule with the total extracts or with the herb in there, and what is the bioavailability? We really don't know what the patient is getting, at least in my mind."** (emphasis added)

Vol. I, pg. 184 Dr. Obermeyer
"I believe the literature would probably support your thoughts." (emphasis added)

This is a member of the FDA staff here implying that the FDA has not done a search of the literature on the amount of ephedra alkaloids which are bioavailable from the actual herb (as opposed to a methanolic extract), let alone done the research themselves! Furthermore this is a tacit admission that these are substantive relevant considerations.

Vol. I, pg. 186 Dr. Dentali
"My understanding is that these products that are the industrial supply for what companies are buying and then placing in the capsule mixed with other ingredients are extracts of water and alcohol, not pH manipulated. So you may have high temperature water, alcohol, and that's why the concentrations typically are not higher than 6 percent..."

This refers to the process currently used to produce the commercially available ephedra herb extracts. These ephedra herb extracts are clearly made in a different way - with a hot methanol/water mixture - than how a consumer would brew tea (no methanol), which in turn is different than direct ingestion of

the actual ground herb, which would not involve the high temperatures used in brewing. Products made with ephedra herb extract are different from products where the actual herb is brewed in hot water, which in turn are different from products where actual ground ephedra herb is ingested without high temperature brewing.

Vol. I, pg. 186 Dr. Jasinski
"So you just put it into a pot and add alcohol and water and you boil it up?"

Vol. I, pg. 186 Dr. Dentali
"Pretty much."

Vol. I, pg. 186 Dr. Dentali
"Evaporate it off, put it on a carrier."

There is much faster gut absorption of the alkaloids when on a carrier (from an ephedra herb extract) as compared to the rate of gut absorption when a person swallows actual ground herb.

Vol. I, pg. 152 Dr. Dentali
"I did happen to come across two studies, and I can get the reference to you and possibly a copy of it. One was conducted in Japan. They had been seeing--they reported seeing a high incidence of adverse effects recently with products containing ephedrine alkaloids. They realized that their data was based on ephedrine and not the extract, and they conducted an animal trial with equivalent amounts of ephedrine alkaloids and comparing the two--in mice, I believe. ... Generally, they found that absorption levels were about half time-wise and the concentrations in the plasma were about half." (emphasis added)

Ephedra herb extract is not ephedrine, and its pharmacological effects are not the same as ephedrine. Most of the products producing serious adverse reactions were abused ephedrine containing products, some misbranded as ephedra herb extract products. It is very common to analyze a so-called ephedra product and find nothing but ephedrine; these products do

NOT contain either ephedra herb extract or ephedra herb.

Vol. I, pg. 276 Jones
"The available data indicates that though ephedra herb shares some of the properties of ephedrine itself, it also possesses beneficial properties in its own right and is furthermore much better tolerated on an alkaloid equivalence basis." (emphasis added)

Vol. II, pg. 80 Mr. Appler
Continues to analyze the Texas reports. He states **"...of the 94 reports in the Poison Control Center for North Texas, there were exactly two that were related to herbal and two others related to ma huang. In every one of those cases, as Dr. Patrick points out, there was no permanent injury of any sort and all the results seen there were mild."** (emphasis added)

Vol. II, pg. 257 Dr. Dentali
"The other area that I feel that didn't receive adequate scientific attention was the differences between the herb, the herb extract, and ephedrine." (emphasis added)

Ephedra herb extract is not ephedrine. Ephedra herb is not ephedra herb extract; the FDA proposed Rule analytical method LIB No. 4053 may be suited to products containing ephedra alkaloids from ephedra herb extract; we will leave comments on this to those who use ephedra herb extract in their products. We use only ephedra herb (no alkaloid extract, no synthetic alkaloids). FDA's proposed analytical method is incapable of accurately measuring the amount of bioavailable ephedra alkaloids contained in the actual herb.

When a consumer drinks a serving of ephedra herb tea - made with the actual herb, not an alkaloid extract - the extraction of the ephedra alkaloids from the herb in the hot water filled teacup is less than when the herb is extracted in a boiling methanol-water solution in an extract factory or in the FDA's proposed Rule analytical method. No consumer uses a boiling hot

methanol-water mixture to make his or her tea.

When a consumer ingests ground ephedra herb in an iced tea that has never been boiled, the extraction of the ephedra alkaloids occurs slowly in the consumer's gut at 37°C, not in a boiling mixture of methanol and water. The FDA's proposed Rule analytical method will greatly exaggerate the real deliverable ephedra alkaloid content of actual ephedra herb products. Remember, the FDA's method was designed to measure the alkaloid content of products made with the alkaloid extract; it has not been validated for products that contain actual ephedra herb (but no alkaloid extract or synthetic ephedrine.)

Because of an arbitrary and capricious failure to consider these relevant facts, FDA must withdraw the Rule, do their homework on analytical methods that are valid for actual ephedra herb products, re-convene the Committee, reach new conclusions that correct these errors, and re-propose a new Rule and a new analytical method.

Alternatively, FDA can exempt from the proposed Rule products that contain actual ephedra herb but do not contain ephedra alkaloid extracts or synthetic ephedrine.

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